DEVELOPMENT OF CATALYTIC SYSTEMS IN BATCH AND FLOW USING DUAL ORGANOCATALYSTS AND SOLID PACKED-BED REACTORS

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DEVELOPMENT OF CATALYTIC SYSTEMS IN BATCH AND FLOW USING DUAL ORGANOCATALYSTS AND SOLID PACKED-BED REACTORS

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This dissertation discusses the development of complex catalytic systems in both batch and flow reactors using either organocatalysts or transition metal complexes with the future goal of developing multicatalyst cascade reactions. The work begins by providing a background of the various uses of multicatalyst systems in cascade reactions in both batch and flow. The observations gleaned from the group's work on the development of a multicatalyst system using a urea catalyst and L-proline in the known α-aminoxylation reaction spurred the development of a proline derivative/urea catalyst system in the formation of not only α,β and β,γ unsaturated enones, but also substituted tetrahydrofuran derivatives. The second chapter illustrates both the scope of the transformation and provides a mechanistic understanding of the system. Then, wanting to transition proline catalyzed reaction to flow without the use of tethered catalysts or expensive soluble proline derivatives, we developed a new method for the direct use of solid proline. A soluble proline pre-catalyst was generated by passing reagents through a packed-bed of proline that was used in a downstream α-aminoxylation reaction. The final chapter extends this idea to the direct use of solid copper (I) oxide in the generation of N-heterocyclic carbene complexes. The utility of the carbene complexes was illustrated in the β-borlyation of α,β unsaturated esters.

BIOGRAPHICAL SKETCH

Suzanne Michelle Opalka (Suzie) was raised in Hollis, NH, a small town in southern NH and attended high school at the Academy of Notre Dame in Tyngsboro, MA. She then traveled to upstate New York to Hobart and William Smith Colleges where she majored in geoscience, chemistry and environmental studies. There, she conducted research with Prof. Brooks McKinney on the occurrence of arsenic in bedrock near Hollis, NH, with Prof. John Halfman developing a calcium budget for Seneca Lake, NY and with Prof. Erin Pelkey developing synthetic methods for making 4-substituted-3-pyrrolin-2-ones. She also spent a summer in Alaska doing paleomagnetic research. Realizing that innovation in chemistry has the potential to mitigate many of humanity's environmental concerns she decided to pursue graduate work in chemistry at Cornell University. She began working in D. Tyler McQuade's lab and continued her research at Florida State University after the group's move to Tallahassee, FL in 2007. Her hobbies include: hiking (preferably in places with mountains and lakes), Irish step dancing, baking and reading.

To my family – you will always be there for me.

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My journey to and through graduate school was made possible by the constant support of many people I could not imagine living without. First I'd like to thank my parents for fostering a sensing of enjoyment for science. From an early age they got up at ridiculous hours to sign me up for summer science classes, and helped me find and apply for camps at science research facilities as I got older. They also let (caught me) making potions in the bathroom with all our cosmetics, toiletries and cleaning supplies and I'm sure had a good laugh when I sold it to our neighbors. Without these early opportunities, I may never have found a path towards chemistry.

The experiences and support of many of my undergraduate professors also influenced my decision to attend graduate school. I'd like to thank my geoscience advisor, Brooks McKinney, for letting me take organic chemistry "for fun", otherwise I would never have completed a chemistry major. I'd also like to thank Erin Pelkey for letting me get my feet wet in his lab and Tara Curtin for providing guidance throughout undergrad and graduate school.

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CHAPTER 1

Increasing Chemical Efficiency in Both Batch and Flow

Abstract

The overarching goal of chemistry is the production of new molecules that result in pharmaceutical agents, bulk chemicals or materials that enhance our life. It is arguable that any molecule a chemist conceives can be synthesized. Reactions that produce compounds used in everyday life, however, must be derived from processes that are economically viable. Thus, developing highly efficient chemical methods is necessary. Additionally, technology that spurs rapid discovery of these highly efficient processes is warranted. This introduction will provide an overview of methods for making reactions more efficient by employing both batch and continuous techniques. Many of the concepts presented in this chapter have provided inspiration for the projects discussed in this thesis.

Introduction

At the UN World Commission on Environmental Development in 1987 there was a call for promoting sustainable development. Sustainable development defined as "Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs"[1] has become a necessary consideration for governments as we experience an increased demand on our finite resources. Additionally, as society places an emphasis on environmental concerns, industries are responding by implementing greener technologies to more cleanly and efficiently produce products that are used in everyday life.

Early on, a set of guidelines, known as the 12 principle of green chemistry, provided recommendations to chemists and engineers on how improve their environmental impact. It was suggested that methods to reduce waste, improve atom economy, use less hazardous chemicals, reduce energy consumption, and implement catalysis be investigated.[2] Chemists and engineers responded by developing metrics to gauge the efficiency of chemical transformations they performed. Efficiency can be measured by an increase in the atom economy of a transformation, a decrease in the number of steps, less waste generation, or decreased time from discovery to scale-up.[3] Many techniques have been developed to address these goals, however, with solvent accounting for a large percentage of waste there is a growing desire to perform more than one reaction in the same vessel. This is not only attractive from a green chemistry perspective, but also from an economic view point. Carrying multiple reactions out in a single vessel eliminates the cost and waste associated with not only each step, but also intermediate work-ups and purifications.[4, 5]

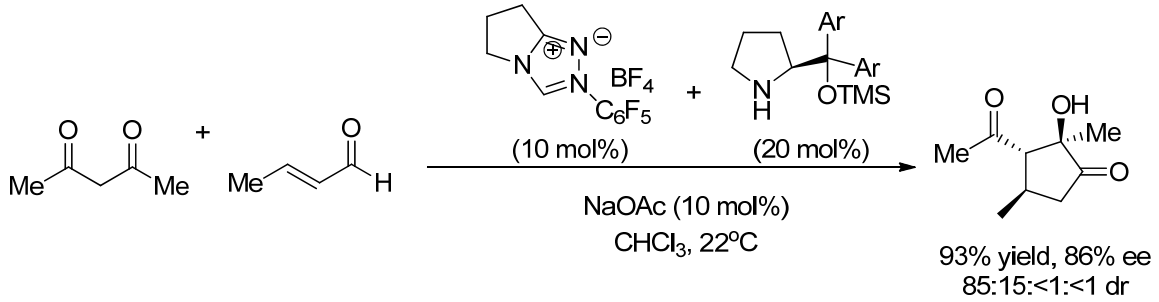
Many chemists look to nature for inspiration on how to become more efficient. Nature produces complex molecules through the assistance of highly efficient enzymatic cascades that produce little waste from start to finish. Furthermore, organisms have evolved over epochs so that hundreds of these reactions can occur simultaneously in the same organism. While research has been dedicated to the implementation of bioengineering in the synthesis of complex molecules[6], organic chemists have been driven to develop their own methods to achieve high complexity in a single reaction flask. Mimicking cascade or domino reaction in the laboratory with simple molecules has proved a great challenge.[7] This chapter discusses some of the strategies used to induce

cascade reactions with single and multiple-catalysts, as well as the use of flow chemistry to afford continuous syntheses of complex molecules.

Improving Batch Processes – Efficient Bond Construction

Cascade Reactions – Compatible Organocatalysts.[7-9] Cascade reactions use a single catalyst or compatible catalysts in one flask to promote a series of reaction steps. Therefore, multifunctional catalysts are often implemented as they can have multiple activation modes to accommodate the necessary transformations. Generally, it has been found that organocatalysts are very tolerant of other reaction conditions. The most widely used modes of action for domino/cascade reactions are iminium/enamine pathways promoted by amine catalysts, hydrogen bonding with ureas, chiral ion pair formation by Brønsted acids, or umplong activation by *N*-heterocyclic carbenes.[7]

One example that clearly illustrates the benefit of telescoping reactions over using an iterative step-by-step approach was presented by Rovis.[10] He combined an amine 3,5-bistrifluromethyl diphenyl prolinol TMS ether catalyst with an triazolium salt *N*-heterocyclic carbene catalyst to initiate a cascade sequence to construct highly functionalized cyclopentanones containing three stereocenters. These compounds were isolated with high diasteroselectivity as well as enantioselectivity. The amine catalyst, a proline analog, was responsible for promoting a Michael addition of the diketone with α,β unsaturated aldehyde. Under one-pot conditions this Michael adduct was directly transformed into the desired cyclopentanone via a crossed aldehyde-ketone benzoin reaction. The authors found 93% yield, 86% ee and high diasterostelectivity for the reaction of acetylacetone and crotonaldehyde (Scheme 1.1).



Scheme 1.1: One-pot multicatalyst approach to the synthesis of subsituted cyclopentanones using amine and NHC-carbene catalysts. TMS=trimethylsilyl, Ar=3,5-$(CF_3)_2C_6H_3$-

When the authors, however, examined this reaction using an iterative process the intermediate Michael adduct was only isolated in 70% yield after reaction with the diphenyl prolinol TMS ether catalyst. Subjection of this product to the *N*-heterocyclic carbene and base catalysts provided 65% yield of the desired cyclopentanone with only 58% ee and 5:1 dr. Upon further study, the authors concluded that when the intermediate Michael product sits in the presence of the amine catalyst a retro Michael product is observed as well as an erosion of enantioselectivity. Thus, employing their multicatalyst cascade sequence directly funnels the highly stereo-pure product to the desired cyclopentanone before this detrimental process occurs, resulting in higher yield and selectivity than the iterative sequence.

Cascade Reactions – Compatible Organo/Metal Catalysts. While the combination of organocatalysts to realize new reactivity has produced many new multicatalyst reactions there is also a movement to combine organocatalysts and metal catalysts to afford even greater diversity in transformations. One popular class of organocatalysts that appear generally more compatible (or at least more studied) with

metal catalysts are Brønsted acids. Cascade reactions with Brønsted acids and metals such as rhodium[11, 12], and ruthenium have been studied.

One example illustrating the utility of this combination is the use of a ruthenium and chiral phosphoric acid catalyst to facilitate a cascade sequence providing polycyclic indoles with high yield and enantioselectivity. The process starts with a ruthenium catalyzed olefin cross-metathesis followed by an asymmetric intramolecular Friedel-Crafts alkylation catalyzed by a chiral phosphoric acid (Figure 1.1). The authors noted that iterative synthesis of the metathesis products normally provided the intermediate in low yield and mixtures of prematurely cyclized products. Thus, continuously converting the metathesis product to the Friedel-Crafts alkylated product allowed for more complete consumption of the starting materials. Again, this example illustrates the use of tandem chemistry and multiple catalysts to more efficiently transform intermediates directly into desired products.

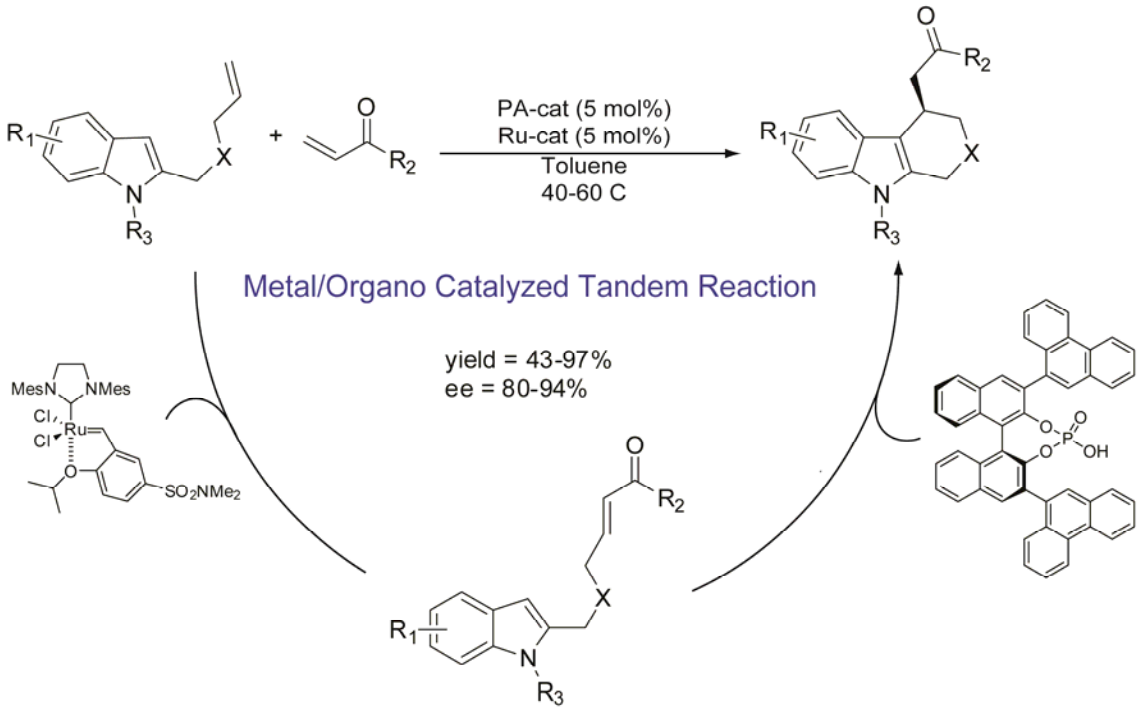


Figure 1.1: The use of a ruthenium and chiral phosphoric acid to perform the tandem synthesis of polycyclic indoles.

Cascade Reactions – Incompatible Catalysts, Site Isolation. Even though combining catalysts in one flask has proven successful, many catalysts are simply not compatible with each other in a single reaction vessel. Traditionally, chemists perform acid/base, oxidation/reduction and organo/metal catalysis in separate flasks as catalyst deactivation by another reaction component is often observed. To address this limitation of cascade/tandem reactions, chemists have developed other ways to site-isolate catalysts without resorting to multiple flasks.[5, 13] Our group developed a dual catalyst system composed of an amine catalyst and nickel based Lewis acid catalyst.[14, 15] Without site isolation, the two catalysts would render each other inactive. Microencapsulation of the amine catalyst via interfacial polymerization, however, readily converted aldehydes and nitromethane to the desired nitroalkene. In the presence of dimethyl malonate and nickel

Lewis acid catalyst the nitroalkene directly formed the desired Michael adduct. Site isolation not only prevented catalyst fowling, but also prevented double addition of the nitroalkane to the nitroalkene by directly funneling the intermediate to the desired Michael adduct, allowing for 65% yield with isovaleraldehyde (Figure 1.2).[14]

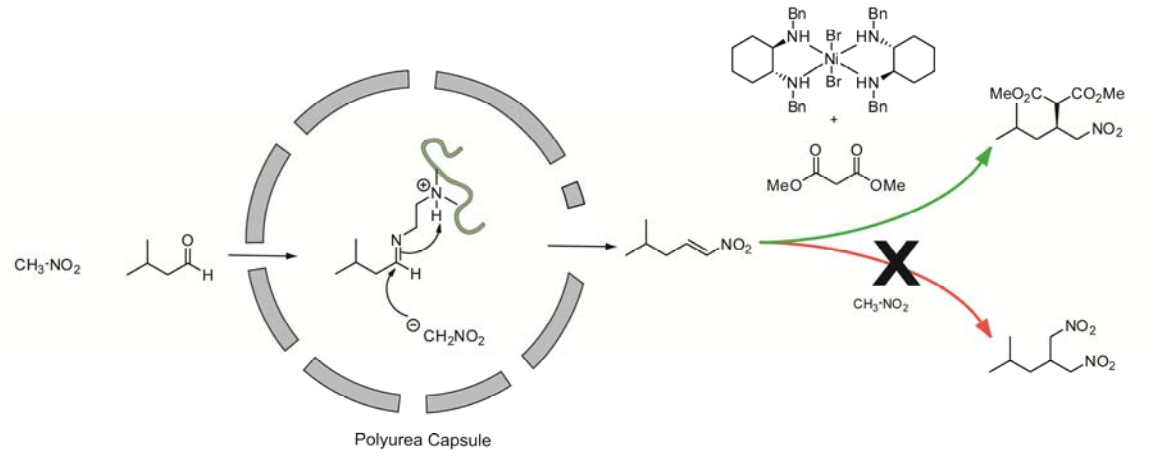


Figure 1.2: Use of microencapsulation to site-isolate an amine catalyst from a nickel based Lewis acid catalyst

As mentioned above, enamine and iminium catalysis are powerful tools employed in cascade reactions. There are instances where optimal enamine and iminium catalysts are not compatible and a step-wise approach is often implemented. Realizing this drawback, Fréchet designed interpenetrating star polymer iminium and enamine catalysts to site-isolate the incompatible catalysts. He was able to carry out an asymmetric cascade reaction employing not only enamine, and iminium catalysts, but also a hydrogen bonding catalyst in the same flask.[16] Under standard one-pot conditions they observed that the small molecule imidazolidinone iminium catalyst and 4-CO_2Et-catechol (hydrogen bonding catalyst), resulted in deactivation of the pyrrolidine catalyst and no

product formation. When the site-isolated star polymer catalysts were employed they observed an increase in yield, but still found that in order to realize 89% yield, 100:8 dr and >99% ee the second pyrrolidine polymer must be added towards the end of reaction to prevent unwanted reaction with the starting 2-hexenal and enamine catalyst (Figure 1.3). This site-isolation technique allowed the cascade reaction of two incompatible organocatalysts to proceed in the same flask and has proven useful in the site-isolation of acid/base catalysts as well.[17]

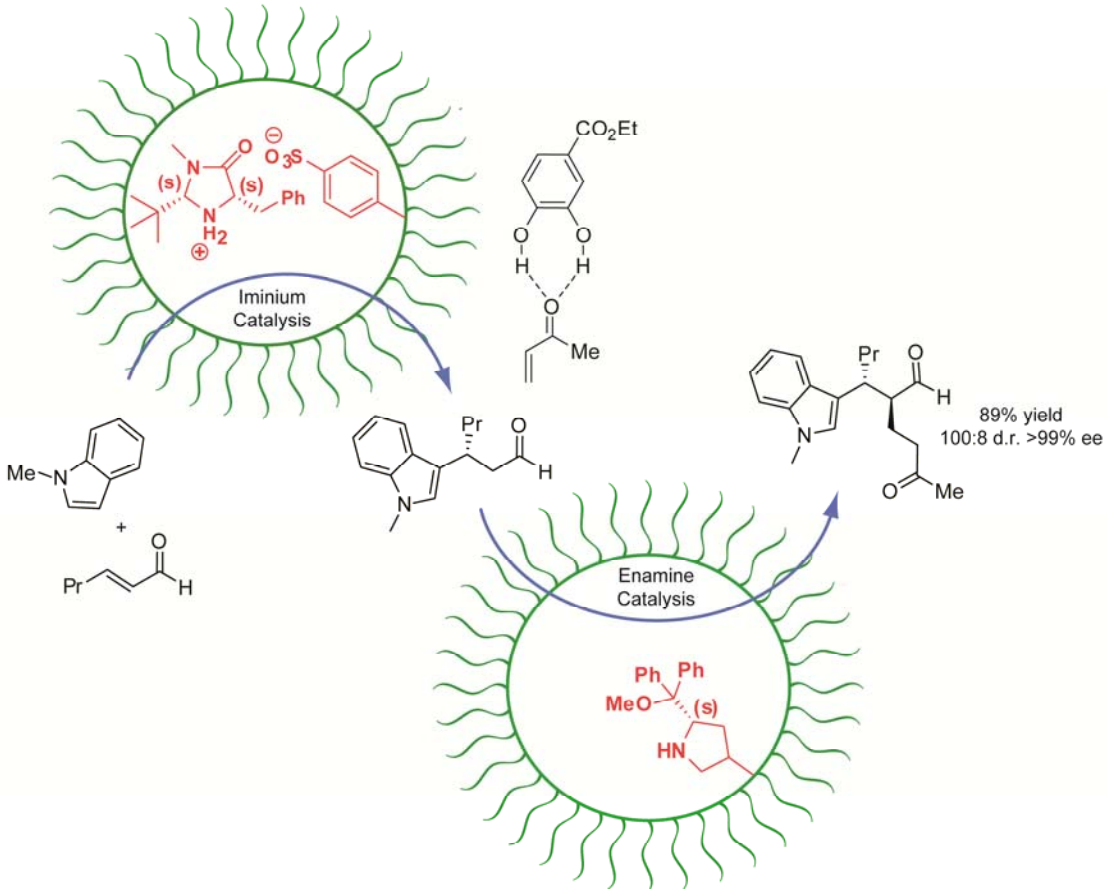


Figure 1.3: Use of star polymers to site-isolate acid/base catalysts

Dual/Synergistic Catalysis – Realizing New Bonds in a Single Flask. While the implementation of multiple catalysts in a single flask to afford a cascade sequence of reactions is a well-established synthetic tool for creating highly functionalized products with little waste, the use of multiple catalysts in one flask to cooperatively or synergistically realize new bond constructions not previously feasible in a single reaction vessel is also a powerful synthetic tool.

The Scheidt group developed a synergistic combination of an *in situ* generated *N*-heterocyclic carbene (NHC) catalyst and Lewis acid catalyst to afford highly substituted γ-lactams from α,β-unsaturated aldehydes and hydrazones.[18] Their approach relied on the combination of the two catalysts to activate the starting materials for reaction. Activation of the aldehyde by the NHC provided a homoenolate nucleophile while the Lewis acid activated the hydroazone through chelation to form an active electrophile. The resulting lowering in energy of the LUMO of the nucleophile and raising of the HOMO facilitated the cyclization reaction (Figure 1.4).

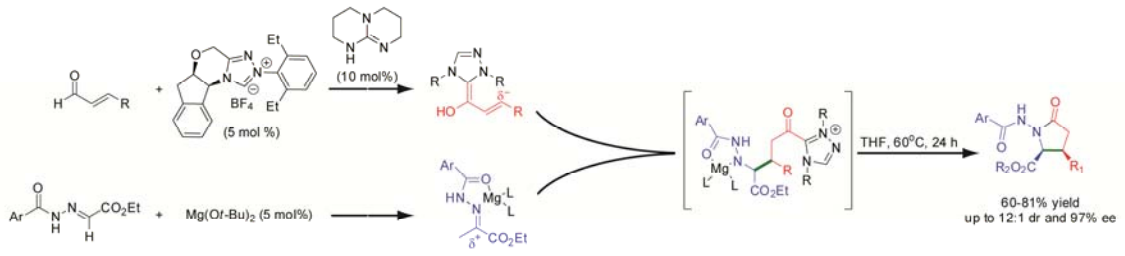


Figure 1.4: Dual catalyst activation of α,β-unsaturated aldehyde by NHC and activation of hydrazone by Lewis acid.

The authors illustrated the utility of their method by providing access to a library of compounds with good yields (60-81% yield), and high diastereo- and enantio-selectivities (up to 12:1 and 98% respectively). This example shows the power of combining two synergistic catalysts in one flask as molecules valuable in the synthesis of pyroglutamic acid, which can be used in the subsequent synthesis of known biologically important molecules, can be prepared. Furthermore, unnatural proline derivatives for use in iminium/enamine catalysis are now accessible using this method.

Many of the techniques described above have provided excellent advances in our understanding of efficient process development, however, the combination of multiple steps and catalysts in one flask adds a complexity that makes optimization of reaction parameters more difficult and time consuming than traditional multi-pot synthesis. One catalyst may perform better at a certain temperature or care must be taken to add reagents in a defined order to direct bond construction. Industry knows that minimizing the amount of time from discovery to scale-up maximizes profits and thus additional strategies must be implement to make cascade-type reactions easier to optimize and scale.

Using Flow Technology

Continuous-flow chemistry[19-21] where reactions are performed in small dimensional channels, is one technology that industry and academia are using for rapid synthesis and scale-up of reactions. Reactions performed in micro to millimeter channels allow for rapid mixing and heat transfer resulting in higher yields, greater productivity and safer handling of toxic materials. This rapid heat transfer has allowed many reactions that are normally performed at cryogenic temperatures to be conducted at higher temperatures thus providing additional cost and energy savings.[22, 23] Furthermore,

transitioning to large scale is performed by simply creating parallel reactors otherwise known as numbering out or by increasing the dimension of the tubing/pipes and adjusting the flow rate to keep the residence times of reagents consistent with those performed in the laboratory setting.[23] Thus the time from discovery to production is greatly reduced.

Early on, as chemists began to embrace this technology, mostly simple one-step reactions were investigated. As flow became more ubiquitous, examples where reactions were linked together in a continuous manner, much like one-pot cascade reactions emerged.[24-27] Within flow chemistry there are a variety of techniques that have been used to string chemical reactions in series. Ideally in this type of setup, multiple reactions are carried out without intermediate work-ups or purifications.[28, 29] Thus, chemists must carefully design reaction sequences to make reactants, products, intermediates, and byproducts compatible with downstream processes. However, sometimes a reaction sequence, with the currently available methods, requires a work-up or purification step. Other methods have been developed to allow for continuous processing of these types of reactions without manual intervention as well. This section will describe a few state-of-the-art multi-step syntheses that are performed in a fully continuous manner.

Improved Synthetic Design - Ibuprofen. One example that our group published that highlights both the careful design strategy that must be implemented to realize multiple steps in a single sequence, as well as some of the touted flow chemistry benefits is the continuous synthesis of Ibuprofen.[30] The reaction sequence commences with a triflic acid mediated Fridel-Crafts acylation of isobutylbenzene with propionic acid at 150ºC and 5 minute residence time. Upon cooling to prevent off gasing, a 1,2-aryl migration in the presence of trimethyl orthofromate (TMOF) and iodosobenzene diacetate

($PhI(OAc)_2$ took place at 50ºC with a 2 minute residence time. The final saponification step combined an cidic solution of intermediate **2** with a concentrated solution of KOH. Fortunately, rapid mixing allowed the fast change in pH to occur without trouble, providing 51% yield of Ibuprofen after recrystallization (Figure 1.5).

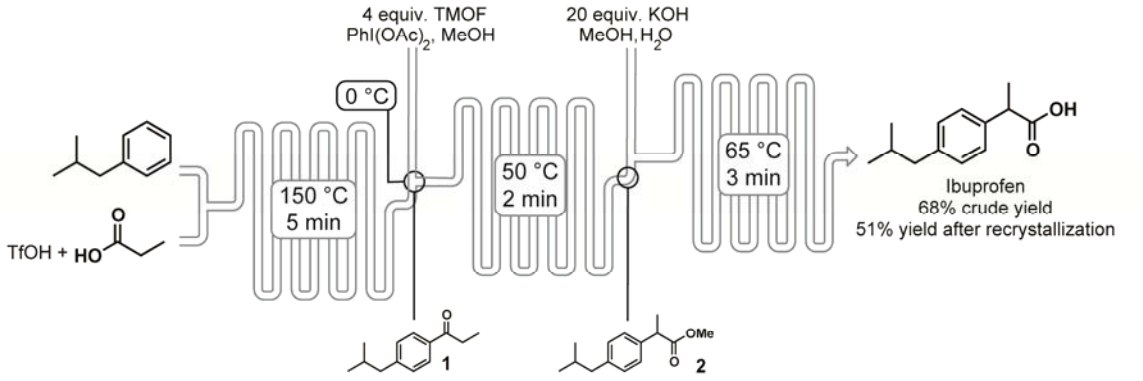


Figure 1.5: Continuous synthesis of Ibuprofen. TfOH = triflic acid, TMOF = trimethyl orthoformate

Improved Synthetic Design - Artemisinin. One of the most highly regarded goals of flow chemistry is the development of reaction routes to highly complex and much needed molecules. Very recently, the Seeberger group designed a method for the continuous total synthesis of artemisinin, a World Health Organization recommended drug used to treat malaria.[31] This disease is widespread in subtropical regions, including many developing nations. Therefore, the synthesis of therapeutic agents must be inexpensive for them to become widely available. Currently, supply is variable because it is currently extracted from the *Artemisia annua* (sweet wormwood) plant.[32]

Artemisinic acid is a more readily available starting material from either a bioengineered process or from the sweet wormwood plant in higher yield. Thus, Seeberger's group used complex intermediate **3** as a starting point in their continuous synthesis of artemisinin. The transformation of artemisinic acid to artemisinin is not trivial. They applied a continuous photochemical reactor the group recently designed[33] to generate photoinduced singlet-oxygen for the oxidation of **3** to intermediate **4**. An acid mediated Hock cleavage results in intermediate **5**. Subsequent oxidation with triplet oxygen and condensation provides artemisinin in 39% yield, with an output of 200g per day from the acid starting material (Figure 1.6). The group calculated that if this process were implemented on 1,500 reactors the demand for this critical drug would be met.

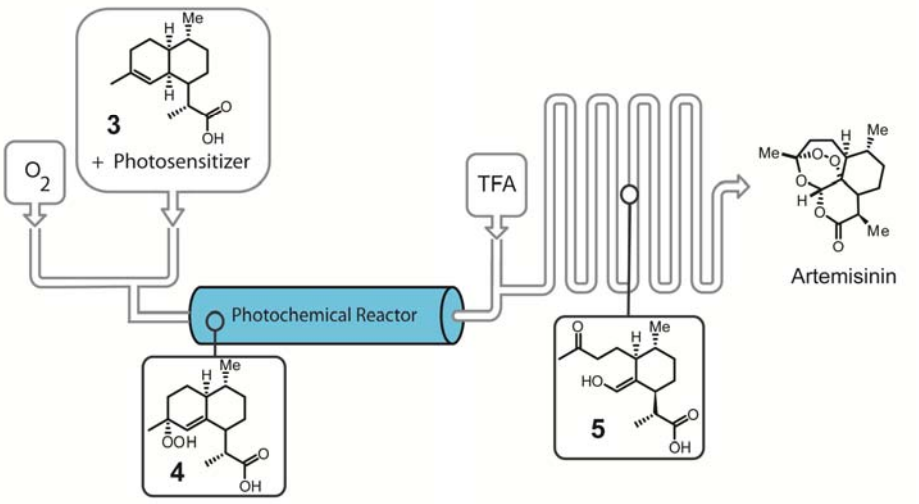


Figure 1.6: Continuous synthesis of artemisinin from artemisinic acid designed by Seeberger.

The syntheses described above are elegant examples of complex continuous syntheses without the need for work-ups or purification steps. Nevertheless, there are

many reactions that require solvent changes, removal of salts or purifications after reaction before follow-up steps can be performed. Numerous enabling technologies have been developed including liquid-liquid extraction, use of supported reagents or catalysts,[34] or more recently in-line distillation[35].

In-line work-up and Distillation - Heck Reaction. Many organic chemistry work-ups rely on liquid-liquid extractions or distillation to remove unwanted byproducts or excess solvents/reagents. Jensen and Buchwald designed a synthesis whereby both a liquid-liquid extraction and distillation were implemented to perform a Heck reaction.[35] Heck coupling reactions are generally between an aryl halide or pseudohalide such as an aryl triflate and activated alkene. Aryl triflates are commonly prepared by reaction of an aryl alcohol with triflic anhydride in the presence of an amine base in a chlorinated solvent. The Heck reaction, however, is generally performed with pure triflates in solvents such as toluene or DMF. Furthermore if the reactions are simply linked together any residual CH_2Cl_2 from the triflate generation would result in decreased yields. Thus, if triflate generation and use in the Heck reaction are combined residual chlorinated solvent must be removed before subsequent use.

In their reactor set-up, the starting phenol was combined with base (DIPEA) and triflic anhydride in dichloromethane. Reaction at 20ºC resulted in the desired triflate. Aqueous HCl was added to establish plug flow to facilitate diffusion of impurities into the water later. Passing the stream through a Teflon membrane separated the CH_2Cl_2/water mixture via selective wetting. To the dichloromethane/triflate stream, DMF and nitrogen gas was added to again establish plug flow, this time between a gas/liquid. The difference in boiling points between DMF and CH_2Cl_2 allowed for diffusion of

CH_2Cl_2 to the gas phase upon heating. Thus, heating the solution in a microfluidic distillation device allowed a nearly pure DMF stream to continue on in the sequence. Addition of coupling partners and palladium catalyst to the triflate stream and subsequent heating to 125ºC resulted in the desired coupled product in 69% yield after hydrolysis to the methyl ketone (Figure 1.7). This example shows the importance of designing in-line aqueous work-up and distillation devices to perform continuous processing. This type of technology has the potential to enable a wider variety of chemistry to be explored in a continuous process.

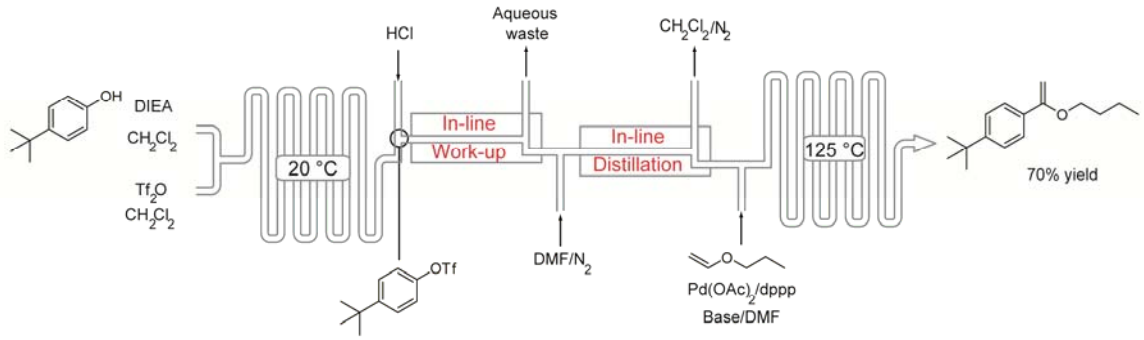


Figure 1.7: Continuous synthesis of aryl triflates for use in downstream Heck coupling, enabled by in-line aqueous work-up and solvent distillation.

Implementing microreactor or batch technology for a given process must be carefully weighed considering the fundamental advantages that each offer.[36, 37] Simply converting processes from batch to flow does not make it innately a better process. It is well documented that reactions requiring enhanced mixing to increase reaction rate or prevent the on-set of side-reactions are better suited to flow.[25, 37] Additionally, the fundamental design of microreactors leads to well modeled systems that provide

increased heat transfer. Heat transfer, either heat removal/addition, can play a critical role in the rate and product distribution of a reaction. Normally batch reactors dissipate excess heat using lower concentrations and temperatures, or slow addition of one reagent. With increased heat transfer flow chemistry allows for harsher reaction conditions to be used that can in turn lead to reduction in resource such as energy to heat/cool or solvent to dilute reactions. However, reactions with long reaction times that do not benefit from additional heating are better suited to batch reactors.

Ascertaining this type of information for a given single-step reaction is often best suited to a combination of batch/flow experiments. Obtaining reaction kinetics or information on possible byproducts before trying a reaction in flow is valuable information as this information is quickly attainable in batch and will influence whether a reaction should be investigated in flow. There are, however, many instances where it is assumed a priori with great confidence that a reaction would benefit from flow. Heterogeneous slurries, for example, would benefit from enhanced mixing if steps to prevent clogging are realized. Furthermore, reactions that use and/or produce toxic or hazardous reagents benefit from flow as a continuous process innately minimizes contact with the reagents. Additionally, it has been found that unstable or moisture sensitive reactions can be generated and used more successfully in flow than in batch. Finally, as shown above, flow chemistry offers advantages in time savings and work-up/purification costs when performing multi-step fully continuous reactions.

Conclusion

Each example in this chapter examines different multi-step synthetic methods using batch reactors using multiple catalysts to perform cascade reactions or carefully

designing and implementing flow chemistry technology to enable continuous, and efficient synthesis. Simultaneous investigation of batch and flow processes will ultimately lead chemists to design more efficient chemical processes. As illustrated above, our group has had an interest in combining multiple-catalysts in one pot or compatible reaction partners to afford new desirable products in batch and flow. This dissertation will discuss both the development of a batch dual multicatalyst system for the construction of substituted tetrahydrofurans as well as the implementation of packed-bed microreactors for the use of solids in flow to synthesize and use homogenous catalysts simultaneously.

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CHAPTER 2

Thiourea/Proline Derivative-Catalyzed Synthesis of Tetrahydrofuran Derivatives: A Mechanistic View

Preface

Upon entering the McQuade group in 2006, the group had recently developed the group's first multicatalyst system that was used in the synthesis of the drug pregabalin. Sarah Poe, and Muris Kobašlija developed an encapsulated amine catalyst that when combined with a nickel catalyst converted nitromethane and aldehydes directly to Michael products by directly funneling the nitroalkene intermediate. Further investigation of this system determined the pendant ureas on the microcapsule surface enhanced the rate of Michael addition by activating the nitroalkene. A small molecule analogue of the urea was synthesized and examined in other reactions for catalytic activity. Upon moving to Tallahassee, the entire McQuade group focused on the proline catalyzed α-aminoxylation of aldehydes that exhibited rate enhancement when combined with the small molecule analogue. The group soon began searching for other proline/urea catalyzed systems. This chapter details the unique reactivity observed in the proline/urea catalyzed aldol reaction and in the synthesis of substituted tetrahydrofurans.

Abstract*

A thiourea/proline derivative-catalyzed synthesis of linear α-substituted tetrahydrofuran/pyran derivatives starting with lactol substrates is presented. This study

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demonstrates the utility and potential complications of using (thio)urea/proline co-catalysis as each of these catalysts is necessary to provide the observed reactivity, but a time-dependent decrease in enantioselectivity is observed. New mechanistic insights into (thio)urea/proline co-catalysis are presented.

Introduction

Proline and secondary amine analogs catalyze a wide range of reactions including aldol[1-3] and Mannich[2] reactions, α-aminoxylations, α-aminations, and α-halogenations[4], to name a few.[5-7] As with many catalysts, proline can benefit from the addition of a co-catalyst such as an acid[8, 9], base[8, 10] or hydrogen bonding species.[8, 9, 11-13] Of the hydrogen bonding co-catalysts, ureas[14] show some of the largest gains in catalytic activity.[15-20]

The role that ureas play in these systems is slowly emerging and appears to be complex and dependent on the structure of the urea.[18, 20] The first example of a urea/proline system used a diarylthiourea to accelerate an aldol reaction. The authors hypothesized that a host-guest complex was formed between proline and urea thereby increasing the solubility of proline. ^{1}H NMR analysis indicated a downfield shift in the urea protons supporting the host-guest complex model.[15] Furthermore, another group used UV and fluorescence data to support that a stable 1:1 complex formed between the catalysts.[17] These early examples have been revisited and it appears that even with simple urea catalysts, the role of the urea is multi-faceted.

More recent mechanistic models now include not only urea/proline catalyst interactions, but also substrate/urea/proline interactions in the transition state. Companyó et al. speculated that the addition of a diarylthiourea enhances the acidity of proline's

carboxylic acid and consequently stabilizes the transition state in the aldol reaction.[17] Recently, our group observed that a urea tethered to a tertiary amine, dramatically increased the rate of the α-aminoxylation and Mannich reactions.[16] We hypothesized that the urea enhanced the rate determining breakdown of the oxazolidinone intermediate yielding the active enamine species. We demonstrated that the nature of the tether and the presence of the tertiary amine were critical parameters.

A similar conclusion was reached by Wang et al. in their study of a chiral bifunctional thiourea/L-proline-catalyzed Michael addition between an aldehyde and nitroolefins.[20] Wang's system is complex as their reaction is also catalyzed by the thiourea alone with high enantioselectivity albeit more slowly. Without the chiral thiourea additive the proline catalyzed reaction had 44% ee; addition of a chiral thiourea led to 90% ee. Switching the absolute configuration of the thiourea, however, had almost no effect on the absolute configuration of the resulting product, indicating that the stereochemistry of the reaction was controlled by L-proline.

While these examples begin to elucidate how ureas and proline interact to affect rate enhancements and alterations in product distribution, continued research into the urea/proline relationship is required to aid in the study and design of other urea/proline-catalyzed reactions. Here, we report a study of a thiourea/proline derivative-catalyzed synthesis of linear α-substituted tetrahydrofuran derivatives. Investigation of this reaction is particularly interesting as neither the proline derivative nor the thiourea can independently catalyze the reaction to any appreciable extent. Through investigation of this reaction, we offer new mechanistic insights into the role ureas play as co-catalysts.

Results and Discussion

Prior Work - Aldol Reaction. From our work on the α-aminoxylation we postulated that a variety of other proline-catalyzed reactions such as the aldol reaction could be accelerated using urea additives. Indeed, our hypothesis was supported by an initial study where we observed that *trans*-4-tertbutyldiphenylsilyloxy (OTBDPS) proline **2a** and urea **1a** accelerated the reaction between 3-phenylpropionaldehyde and acetone. Examination of the data shown in Figure 2.1 (A) revealed that the reaction rate was accelerated in the presence of both **2a** and **1a**. We were surprised to observe that the product distribution for the proline derivative **2a** alone and the combination of **2a**/**1a** were different. The **2a** alone case produced **3** in vast majority, as has been previously noted by List and Wang, independently.[21, 22] In contrast, the **2a**/**1a** system produced **4**, a previously unreported byproduct in the aldol reaction, as the major product and **3** as the minor component (Figure 2.1 (B)). Additionally, once the starting material was consumed **4** was converted to **3**.

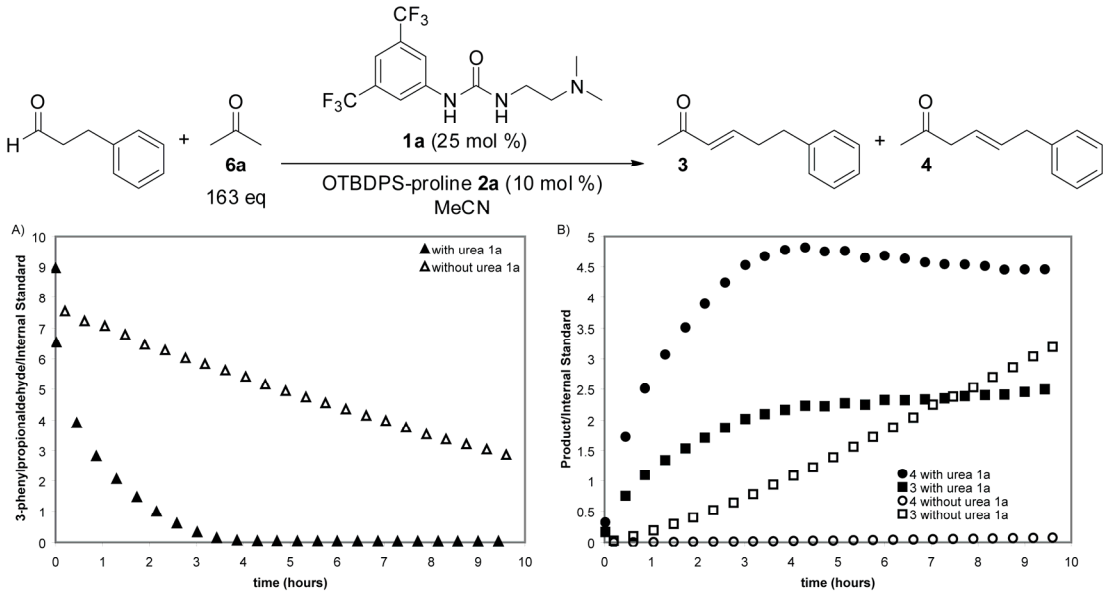
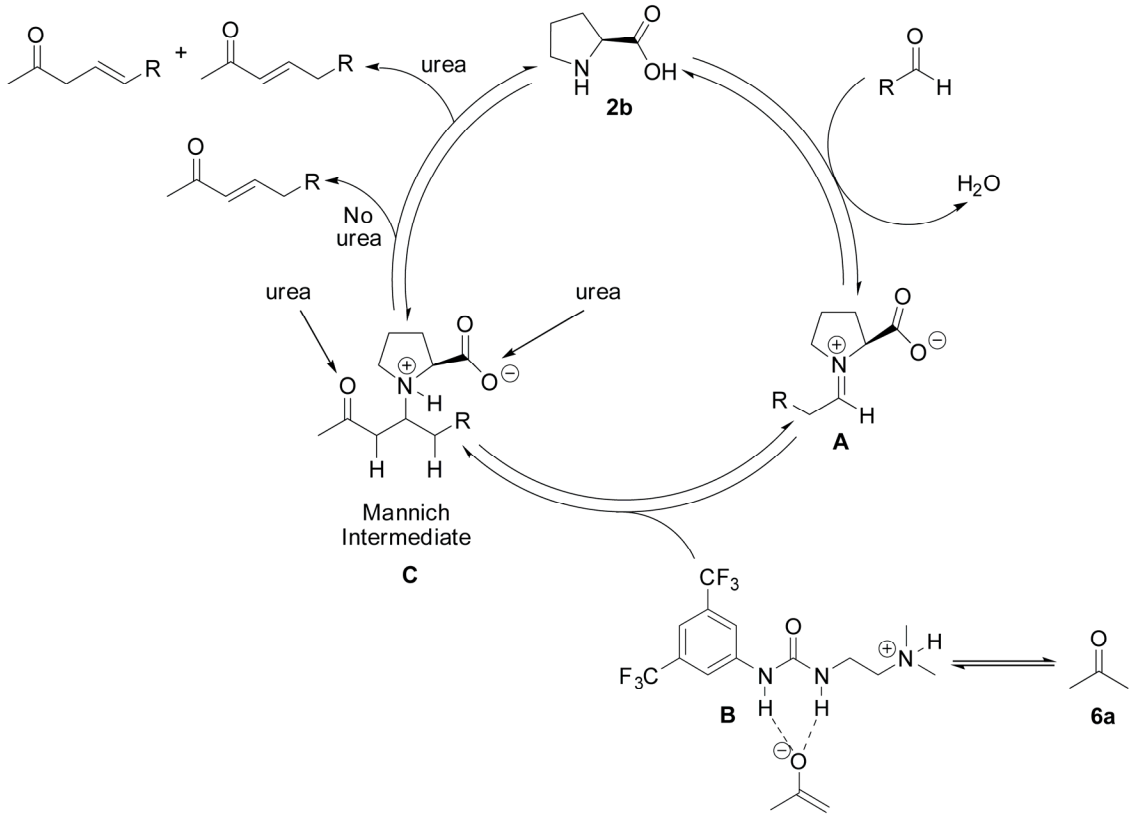


Figure 2.1: Reaction profiles for the aldol condensation reaction between 3-phenylpropionaldehyde and acetone. A) Starting material consumption B) Appearance of products.

The observation that the combination of **2a**/**1a** yielded **4** prompted us to develop a new model (Scheme 2.1). We propose an extension of the "Mannich condensation"[23] mechanism described by List for the formation of enone byproducts in the aldol reaction.[21] The catalytic cycle begins with the activation of the aldehyde by proline (or proline derivative) to give **A**, followed by the addition of acetone and subsequent elimination of proline from "Mannich Intermediate" **C** yielding the α,β-enone via the proline-only path. We propose that the addition of the urea accelerates the cycle by activating the enol form of acetone (**B**) that reacts with **A**. The observed alteration in product distribution in the presence of the urea is justified through the binding to

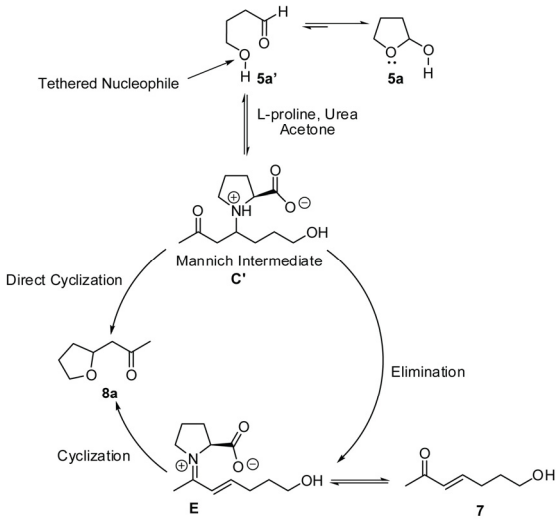
intermediate **C**. Subsequent deprotonation by the pendant amine on the bifunctional urea finally gives rise to both the α,β and β,γ-enones.



Scheme 2.1: Proposed Mechanism for Observed Elimination Products

While the model provided a reasonable explanation for the altered product distribution in the presence and absence of the bifunctional urea, it did not provide insight into how to favor the formation of **3** or **4**. The model did, however, offer clues as to how we might use the Mannich Intermediate to produce cyclic ethers using substrates with tethered nucleophiles (Scheme 2.2). We envisioned two possible routes, each beginning with activation of the ring-opened form of 2-hydroxytetrahydrofuran **5a** with L-proline and acetone to give Mannich Intermediate **C'**. We hypothesized that cyclization would

occur when the tethered nucleophile displaced proline via either direct S_N2 substitution of the Mannich Intermediate (**C'**) or Michael addition of **E** (Scheme 2.2).



Scheme 2.2: Proposed Use of the "Mannich Intermediate"

Verification of Proposed Cyclization and Optimization of the Reaction. We tested the hypothesis articulated in Scheme 2.2 using the reaction between 2-hydroxytetrahydrofuran **5a** and methyl propyl ketone **6b**. Monitoring product formation as a function of time using the catalyst combination **2a**/**1a**, we observed that the reaction was rapid, finishing with ~80% yield (Figure 2.2). The rate profiles observed were not asymptotic, suggesting complex kinetics. The plot of enantioselectivity as a function of time also underscores the complexity of the reactions, as it exhibits three distinct profiles. The enantioselectivity of the reaction was initially high and constant for the first hour, rapidly decreased during the second hour, and then slowly decreased after consumption of starting material (Figure 2.2).

In an effort to understand the change in enantioselectivity as a function of time and to potentially improve the enantioselectivity, we studied the influence of the urea and

proline structure on the reaction. To begin, we examined the importance of the urea as an additive in the reaction and then the structural features of the urea that influenced the reaction yield and enantioselectivity.

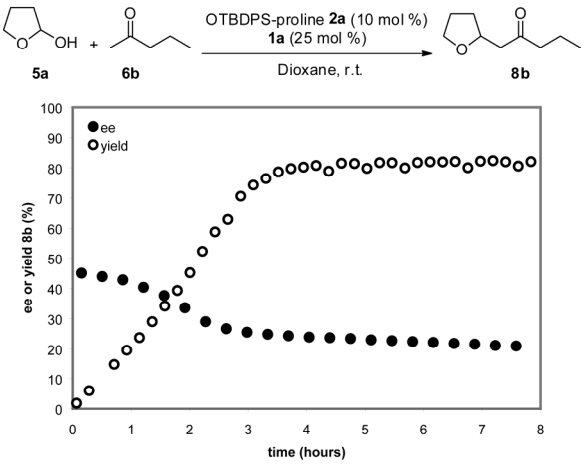
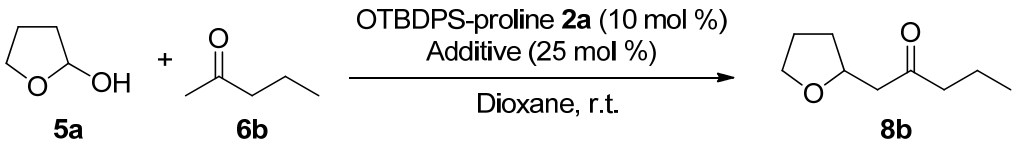


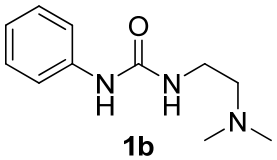
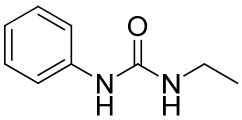
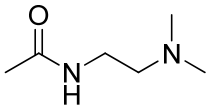
Figure 2.2: Reaction of 2-hydroxytetrahydrofuran and methyl propyl ketone in the presence of urea **1a** and proline derivative **2a** in 1,4 dioxane. Reaction profile and enantioselectivity profile for 10 mol % OTBDPS-proline **2a**.

From entry 1 (Table 2.1), we determined that **2a** alone could not catalyze the reaction. In addition, use of **1b** alone resulted in less than 1% yield after 27 hours (data not shown). From these data, we concluded that both the urea and the proline derivative were necessary components in this reaction. We then performed a structure activity relationship study to isolate which features of the urea were necessary. We found that both the urea functional group and a tethered amine were critical features (Table 2.1, entries 2-6). We observed that amide **9** catalyzed the reaction but with a lower overall yield at 28 hours (Table 2.1, entry 4) and that **2a** (10 mol %), urea **1c** (25 mol %), and

amine **10** (25 mol %) exhibited a slower rate and lower enantioselectivity (Table 2.1, entry 6), demonstrating the necessity of a bifunctional catalyst such as **1b**.

Table 2.1: Influence of Additives



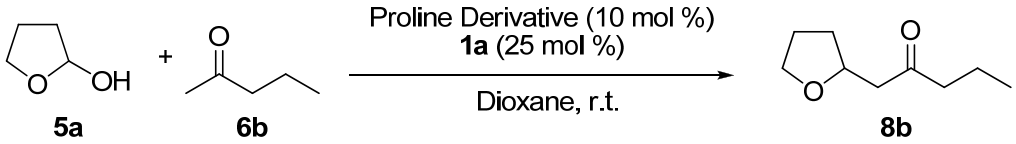
Entry	Additive	Yield (%)[a]	ee (%)[b]	Time (hrs)
1	None	<1	ND	26
2[c]	 **1b**	75	34	6
3	 **1c**	<5	ND	26
4	 **9**	31	51	28
5	 **10**	<5	ND	27
6	**1c +10**	69	5	29

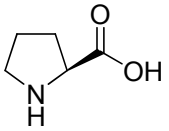
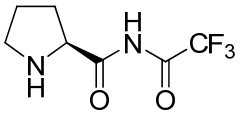
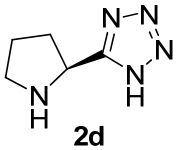
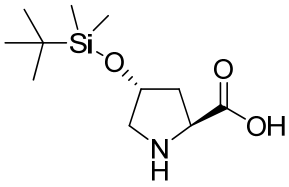
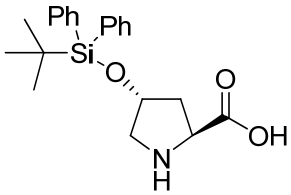
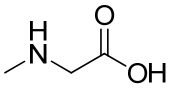
[a] Determined by GC analysis using mesitylene as an internal standard. [b] Determined by GC analysis within 4 hours of deeming reaction complete. [c]Without OTBDPS-proline **2a,** reaction with **1b** has less than 1% yield in 27 hours as determined by GC analysis. ND=Not determined

We also studied the structural features of the proline derivative required for this transformation. The reaction did not proceed using proline derivative **2c** (developed by Wang for the construction of α,β enones, Table 2.2, entry 2),[22] tetrazole proline derivative **2d** (Table 2.2, entry 3), or N-methylglycine (Table 2.2, entry 6). We observed that only carboxylate-containing proline derivatives catalyzed the reaction and that 4-silyloxy-

substituted proline derivatives provided the fastest reaction rates (Table 2.2, entries 1,4-5). We found that OTBDMS-proline derivative (**2e**), provided not only a faster rate but also a faster decrease in enantioselectivity relative to the OTBDPS-proline derivative (**2a**) (Figure 2.3).

Table 2.2: Influence of Catalyst Structure



Entry	Catalyst	Yield (%)[a]	ee (%)[b]	Time (hrs)
1	 **2b**	74	38	42
2	 TFA **2c**	NR	NA	42
3	 **2d**	<5	ND	42
4	 **2e**	77	19	3
5	 **2a**	74	27	4
6	 **2f**	NR	NA	24

[a]Determined by GC analysis using mesitylene as an internal standard. [b]Determined by GC analysis within 4 hours of deeming reaction complete. NR = No reaction; ND=Not determined; NA=Not applicable

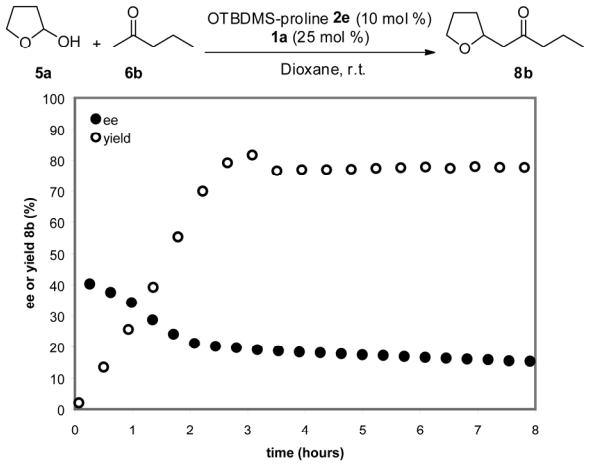


Figure 2.3: Reaction of 2-hydroxytetrahydrofuran and methyl propyl ketone in the presence of urea **1a** and proline derivative **2e** in 1,4 dioxane. Reaction profile and enantioselectivity profile for 10 mol % OTBDMS-proline **2e**.

We then studied how the concentration of **2a** influenced the reaction's enantioselectivity. Interestingly, decreasing OTBDPS-proline **2a** loading to 5 mol % provided a 10% rise in the initial enantioselectivity of the reaction along with a 10% higher enantioselectivity at the conclusion of the reaction (Figure 2.4).

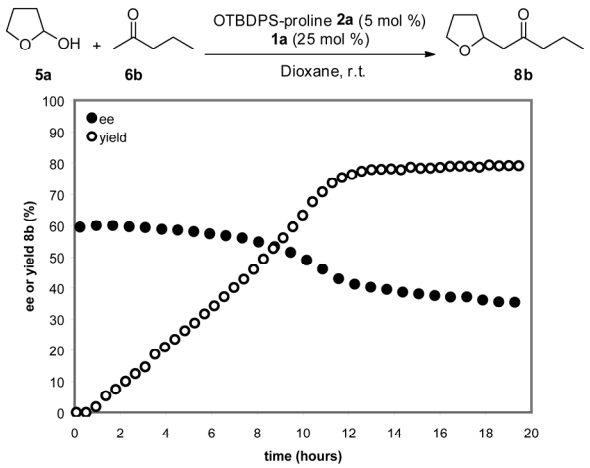


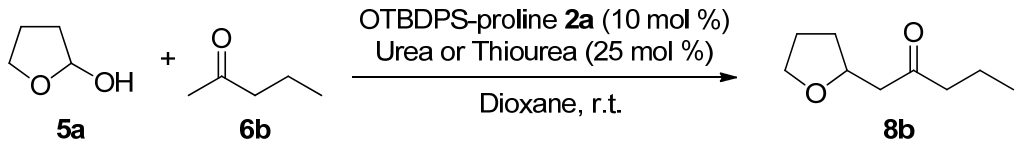
Figure 2.4: Reaction of 2-hydroxytetrahydrofuran and methyl propyl ketone in the presence of urea **1a** and proline derivative **2a** in 1,4 dioxane. Reaction profile and enantioselectivity profile for 5 mol % OTBDPS-proline **2a**.

Finally, we concluded the catalyst structure study by examining the influence of different bifunctional ureas on the reaction. A suite of ureas and thioureas related to **1b,** including Takemoto's catalyst[24] (Table 2.3, entries 7 and 8), was examined. We found that electron withdrawing groups lead to enhanced reaction rate, but decreased enantioselectivity (Table 2.3, entries 1 and 2) while using a thiourea resulted in only small gains in enantioselectivity (Table 2.3, entries 1,3 and 4,5). A longer linker between the urea and amine showed almost no change in rate or enantioselectivity (Table 2.3, entries 3,5 and 1,4), but increasing the steric bulk around the amine led to a slower reaction rate and decreased enantioselectivity (Table 2.3, entry 6). Optically active ureas did not improve the yield or enantioselectivity (Table 2.3, entries 7 and 8).

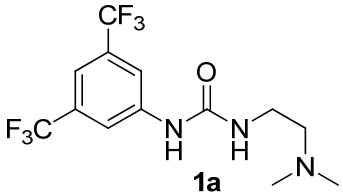
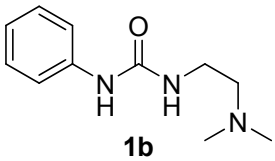
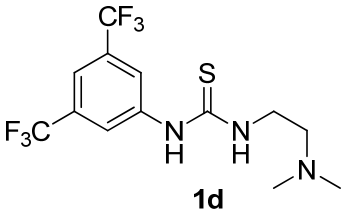
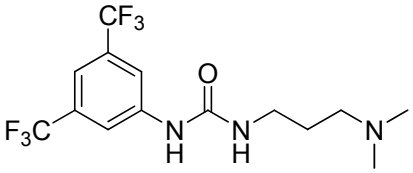
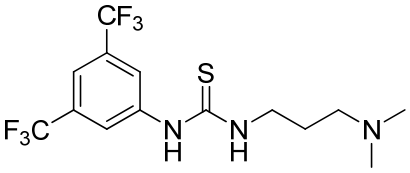
From these data and those presented above, it is clear that both the proline derivative structure as well as structure and electronic properties of the urea are important

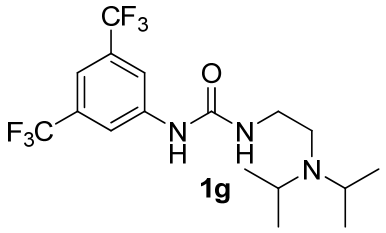
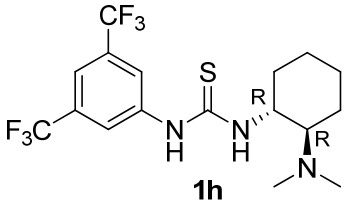
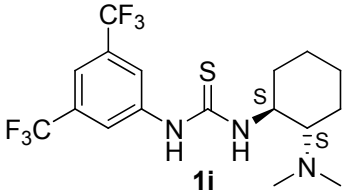
factors influencing the yield, though no catalyst combination has yet to provide high enantioselectivity.

Table 2.3: Influence of Urea Structure



5a 6b 8b

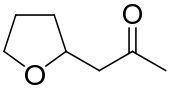
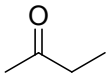
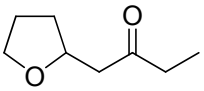
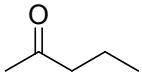
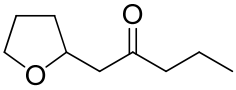
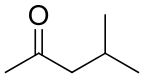
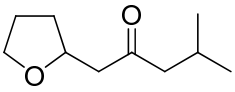
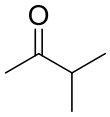
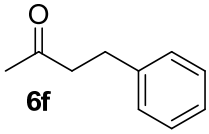
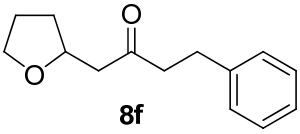
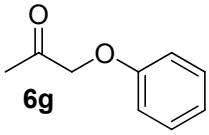
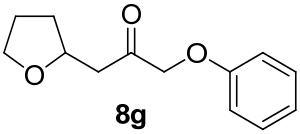
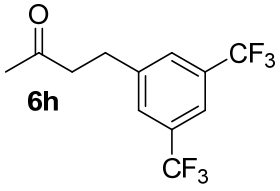
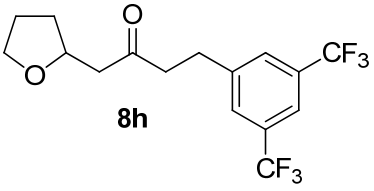
Entry	Additive	Yield (%)[a]	ee (%)[b]	Time (hrs)
1	 1a	74	27	4
2	 1b	75	34	6
3	 1d	74	36	4
4	 1e	74	27	5
5	 1f	74	35	5

6	 **1g**	71	6	9
7	 **1h**	73	34	22
8	 **1i**	74	34	9

[a] Determined by GC analysis using mesitylene as an internal standard. [b]Determined by GC analysis within 4 hours of deeming reaction complete.

Using the optimized catalyst system **2a/1f**, we proceeded to evaluate the substrate scope with a variety of aliphatic ketones to determine which substrate structural biases exist and if the observed low enantioselectivities were a general feature of this method. We found that indeed enantioselectivities were low, ranging from 0-48% for the substrates studied (Table 2.4, entries 1-8, see supporting information). Aliphatic ketones were easily transformed to the corresponding cyclized products (Table 2.4, entries 1-4), though the ketone must be flanked by a methylene (Table 2.4, entry 2 versus entry 5). Ketones with flanking aryl ethers and benzylic groups also exhibited modest to high yields (Table 2.4, entries 6-8). From these data, we conclude that this dual catalyst method is an efficient strategy for construction of the C-C bond, but that the system does not provide high enantioselectivity.

Table 2.4: Scope of Substitution of 2-hydroxytetrahydrofuran with Ketones

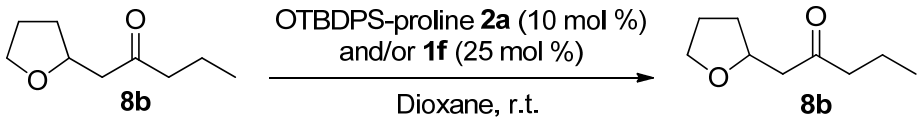
Entry	Ketone	Product	Yield (%)[b]	Time (hrs)
1[a]	 6a	 8a	40	4
2	 6c	 8c	78	6
3	 6b	 8b	81	5
4	 6d	 8d	69	8.5
5	 6e	NR	NR[c]	58
6	 6f	 8f	76	5
7	 6g	 8g	84	22
8	 6h	 8h	73	12

[a]Reaction run in CH_2Cl_2 due to high volatility of product; [b]Isolated yield; NR = No reaction; NA=Not applicable. [c]200µmol reaction run with catalyst **2a** and **1a** in CH_2Cl_2, after 58 hours GC analysis indicated the presence of mostly starting lactol. Enantioselectivities ranged from 0 to 48%, see supporting information.

Origin of decreasing enantioselectivity.

Prior to our work, the important mechanistic observation of decreasing enantioselectivity with time had not been reported in proline/urea co-catalyzed systems. We postulated initially that the decrease in enantiomeric excess was due to rapid product racemization. The configurational stability of **8b** was assessed by subjecting pure product with 33% enantiomeric excess to various catalyst combinations. Table 2.5 presents changes to the enantiomeric excess as a function of conditions over 36 hours. We observed that the enantiomeric excess remains constant in the presence of thiourea **1f** or OTBDPS-proline derivative **2a** (Table 2.5, entries 1,2) alone, but that the combination of the two caused a decrease from 33% to 4% enantiomeric excess in 36 hours (Table 2.5, entry 3). These data indicate that slow erosion of ee once starting material was consumed can be explained by racemization of the product, but these data do not explain the rapid decrease in enantiomeric excess during the first phase of reaction (between 1 and 2 hours). Addition of methyl propyl ketone did not alter this behavior.

Table 2.5: Influence of Catalyst(s) on Enantiomeric Excess of 8b



Entry	Catalyst(s)	ee after 36 hours (%)[a]
1	OTBDPS-proline **2a**	33
2	Thiourea **1f**	33
3	OTBDPS-proline **2a** + thiourea **1f**	4

[a]Determined by GC analysis with an initial enantiomeric excess of 33% for the product. No evidence of product decomposition detected – see supporting information.

We sought an experiment to help us explain the rapid decrease in enantioselectivity observed between the first and second hour of the reaction. Our original mechanistic model, as well as the model in the gold-catalyzed synthesis of substituted tetrahydropyrans from homopropargylic ethers, suggests an α,β enone as a potential intermediate for Michael-type cyclization strategies.[25] When enone **7** was subjected to our catalyst conditions, we found that both **1a** and **2a** alone catalyzed the ring closure of **7**. The rate of cyclization, however, was enhanced when both catalysts were used together (Figure 2.5). This observation indicates that **7** might be an intermediate along the reaction coordinate leading to the cyclization product. When we examined the configuration of **8a** when **7** was cyclized by **2a**/**1a**, we observed that the opposite enantiomer (-8% ee measured at 7.5 hrs) resulted compared to when lactol **5a** and acetone were cyclized in the presence of **2a** and **1f**.[26] As discussed below, we propose a mechanism whereby cyclization of intermediate **7** is competing with another cyclization mechanism and that the maximum rate of decreasing enantiomeric excess occurs when the two paths are operating simultaneously.

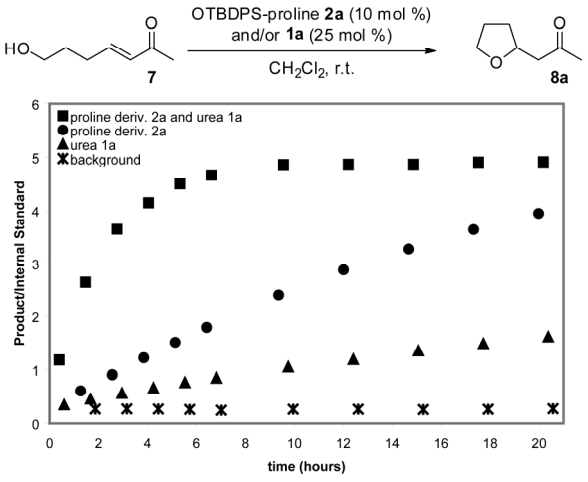


Figure 2.5: Subjection of enone **7** to catalyst conditions.

Before finalizing our mechanistic model, we determined if a nonlinear effect existed in our system. Nonlinear effects in proline-catalyzed reactions have been studied in a number of contexts.[18, 19, 27, 28] Though the reaction types differ, it is clear that the observation of nonlinear effects suggests that the active catalyst species is a complex of one or more species.[29]

We selected proline to study nonlinear effects because both enantiomers are commercially available. We examined the enantiomeric excess of our reaction as a function of L-and D-proline mole fraction. A small positive nonlinear effect was observed. When combined with our rate and decreasing enantiomeric excess with time data, these experiments suggest a complex composite mechanism for this reaction.

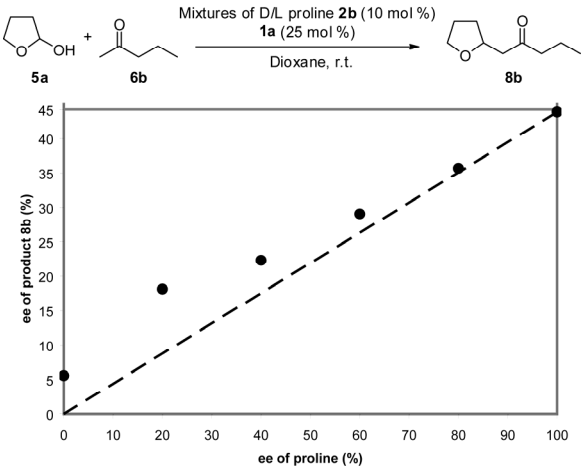
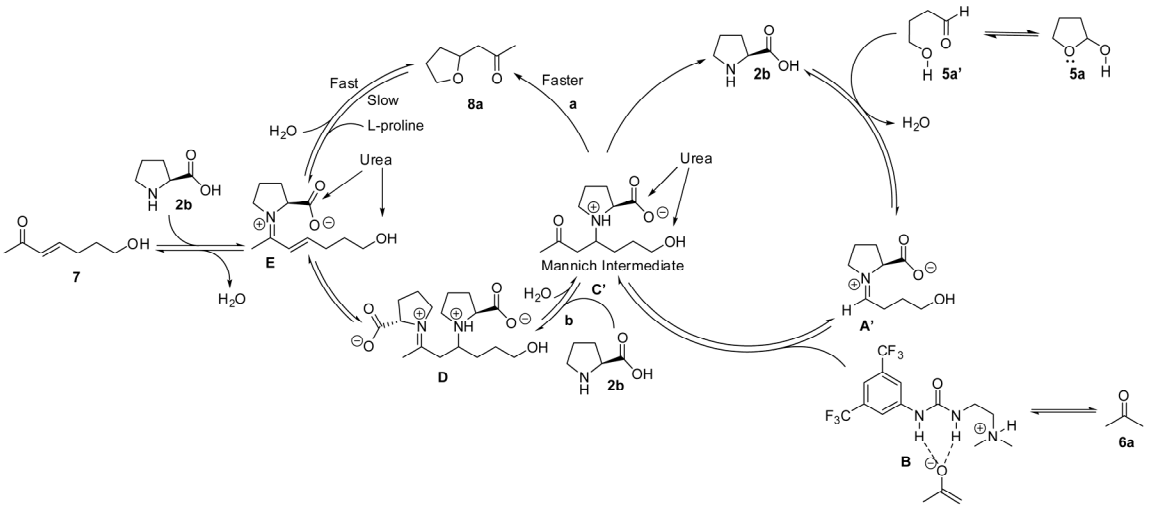


Figure 2.6: Relationship between the enantioselectivity of the product **8b** and the enantiomeric excess of proline. Dashed line indicates expected enantiomeric excess of product. Samples were withdrawn, diluted into dichloromethane and analyzed for enantioselectivity at 22 hours before completion of the reaction.

Proposed Mechanism. With evidence for dramatic loss of enantioselectivity during the course of the reaction (Figure 2.2, 0-2 hrs), a much slower loss of enantiomeric excess after the reaction is complete (Figure 2.2, >2 hrs), and erosion of enantioselectivity when purified **8b** is subjected to reaction conditions (Table 2.5) and the nonlinear effect observed (Figure 2.6), we propose a model with two intertwined catalytic cycles with a common intermediate (Mannich Intermediate **C'**; Scheme 2.3) that can proceed down two pathways. Our model is an extension of mechanisms proposed by List, Cordova, Pihko, and Zeitler/Gschwind for aldol and Mannich condensation reactions.[21, 30-32] Starting from the upper right corner, **5a'** reacts with L-proline to give iminum **A'**. A urea-activated ketone **B** then adds to **A'** to give common Mannich Intermediate **C'**.



Scheme 2.3: Proposed Mechanism

The rapid loss of enantioselectivity with time (Figures 2.2, 2.3, 2.4) forced us to consider multiple pathways for **C'**, with one path dominating in the first phase of the reaction and an alternative path whose rate increases as a function of changing reaction

conditions. In the dominant early path, we propose the urea binds to the carboxylate anion in **C'** as is speculated for many urea-catalyzed processes.[33, 34] The tethered amine then deprotonates the alcohol leading to direct cyclization exhibiting high enantioselectivity (Scheme 2.3, route a, Figure 2.7(A)). At high aldehyde/lactol **5a** concentrations (first hour), we propose that the proline is largely bound to the starting material. Once the lactol concentration decreases, the increase in free proline opens the diproline pathway (intermediate **D**) that proceeds through enone **E**. This causes a subsequent drop in the enantiomeric excess because the enone pathway provides the opposite enantiomer, as we observed when **7** was subjected to reaction conditions.

This model is supported by our observation that a decrease in the initial proline derivative concentration from 10 mol % to 5 mol % resulted in a 10% greater initial enantioselectivity. These data suggest that the second order in proline path is suppressed when the total proline-derivative concentration is low. In addition, the observed non-linear effects observed suggest that a diproline-derivative path is possible. Finally, others have reported that diproline intermediates are present in aldol condensation reactions[30, 31] (as well as other proline-catalyzed reactions).[35, 36]

Most recently Zeitler and Gschwind used NMR to investigate the mechanism of the proline-catalyzed aldehyde self-condensation. The researchers observed differences in the rate of formation for the aldol product versus aldol condensation product (elimination products similar to those observed in Figure 2.1, compounds **3** and **4**) when varied catalyst loadings were used. From these experiments, the authors support the earlier mechanistic work that the aldol condensation utilizes two proline molecules in the rate determining step.[32]

In our case, we hypothesize that the urea binds to the less hindered proline diproline adduct present in intermediate **D**. Deprotonation of the alpha hydrogen results in α,β elimination product **E** with a single proline still bound (Scheme 2.3 route b, and Figure 2.7(B)). **E** then cyclizes to give product **8a**. Thus, the observed rapid loss of enantioselectivity between hours 1 and 2 is the result of the elimination pathway operating at a different rate than the direct cyclization pathway. The slow erosion of enantiomeric excess after the lactol is consumed is due to product racemization (Scheme 2.3). Likewise, Zeitler/Gschwind attributed the erosion of diastereoselectivity during the proline-catalyzed aldehyde self-condensation to the changing rates of aldol addition, aldol condensation, and retro-aldolization reactions.[32] In addition, Massi et al. observed epimerization of α-C-glycosylmethyl ketones in the presence of proline. These authors propose an intermediate similar to **E** shown in Scheme 2.3.[37]

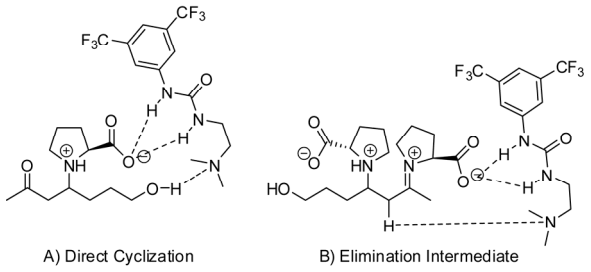


Figure 2.7: Possible interactions of urea with Mannich Intermediate to provide A) direct cyclization or B) α,β elimination intermediate.

Conclusion

We developed a dual organocatalyst system using a bifunctional thiourea and proline derivative to efficiently catalyze the formation of α-substituted tetrahydrofuran/pyran derivatives. Decreasing enantioselectivity and complex reaction

kinetics led us to propose that the thiourea/proline system operates via two competing reaction routes. We proposed one route that dominates at the beginning of the reaction and involves direct cyclization of a Mannich-like intermediate, providing moderate enantioselectivity. As the reaction proceeds, free proline becomes available, and a second diproline intermediate based pathway that produces the opposite enantiomer begins to dominate. Upon completion of the reaction, product racemization occurs resulting in continued erosion of enantiomeric excess by the dual catalyst system. Currently, this method operates with moderately high yields; we believe it can be made highly enatioselective once catalysts that can divert the pathway to one dominant mechanism are designed.

Acknowledgements. The authors thank NSF (CHE-0809261), NDSEG (SMO) and FSU for startup support. Additionally, we thank the FSU Vice-President of Research, and the Dean of Arts and Sciences for upgrading the NMR facility

Experimental Section

1.1 General Information

Catalyst screening reactions were performed in 2mL vials and reactions monitored by gas chromatography by direct sampling of the stirred reaction vials. Glass, gas tight syringes were used to transfer air and moisture sensitive liquids. Flash chromatography was performed using silica gel (230-400 mesh). For analytical thin layer chromatography (TLC), silica gel 60 F_{254} plates were used. All commercial reagents were used without further purification with the following exceptions: dichloromethane for air sensitive reaction was dried by passing through columns packed according to the procedure of Timmers.[38] Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 600 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Data are represented as follows: chemical shift, multiplicity (br. = broad, s=singlet, d=doublet, t=triplet, q=quartet , m=multiplet), coupling constants in Hertz (Hz), integration.

1.2 Instrumentation

Gas chromatographic (GC) analyses for substituted tetrahydrofuran synthesis experiments were performed using a GC equipped with an autosampler, a flame ionization detector (FID), and a column with dimensions 30 m x 0.319 mm x 0.25 μm. The temperature program for GC analysis held the temperature constant at 80ºC for 1

min, heated samples from 80 to 250ºC at 25 ºC/min and held at 250ºC for 2 min. Inlet and detector temperatures were set constant at 250 and 300ºC, respectively. For α,β β,γ work the analysis held the temperature constant at 80ºC for 1 min, heated the samples from 80 to 200ºC at 17 ºC/min held at 200ºC for 1.94 min. Inlet and detector temperatures were set constant at 220ºC and 250ºC, respectively. Mesitylene was used as an internal standard to calculate reaction conversion and calibrate yields.

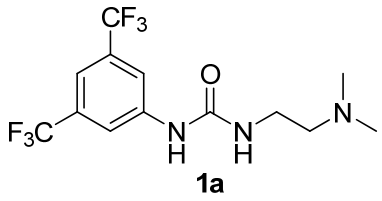
We previously reported the synthesis of **1b**[16]

Wei Wang Catalyst **2c** was prepared following literature procedure and the ^{1}H NMR spectrum matched the previously reported spectrum.[22]

Lactol **5a** was prepared following literature procedure and the ^{1}H NMR matched the previously reported spectrum.[39]

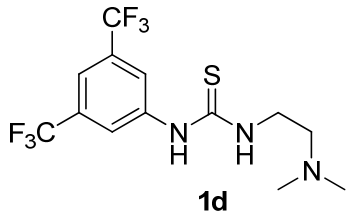
2. Experimental Methods

2.1 Amine/Urea/Thiourea Preparation



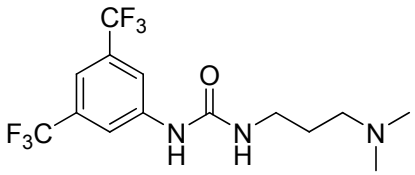
1a

1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-(dimethylamino)ethyl)urea 1a. To a solution of 3,5-bis(trifluomethyl) phenyl isocyanate (0.50 mL, 2.90 mmol, 1 eq) in ethyl acetate 30 mL was added N,N'-dimethylethylenediamine (0.35 mL, 3.19 mmol, 1.1 eq). The reaction was stirred at room temperature for 24 hours and then concentrated *in vacuo.* The crude product was then recrystallized from 10% ethyl aceate/90% hexanes and washed with cold hexanes to yield **1a** (0.55 g, 55%) as white crystals. Mp 137-139ºC. ^{1}H NMR: (600 MHz, CD_3OD) δ 8.02 (s, 2H), 7.50 (s, 1H), 3.37 (t, J=6.54 Hz, 2H), 2.52 (t, J=6.51 Hz, 2H), 2.32 (s, 6H) ppm.^{13}C NMR (150 MHz, , CD_3OD) δ 157.4, 143.5, 133.2 (q, J=32.99 Hz), 124.9 (q, J=271.75 Hz), 119.0, 115.4 (m), 59.8, 45.5, 38.5 ppm. Anal. Calcd. for $C_{13}H_{15}F_6N_3O$: C: 45.49, H: 4.40, N: 12.24. Found C: 45.49, H: 4.30, N: 12.20.



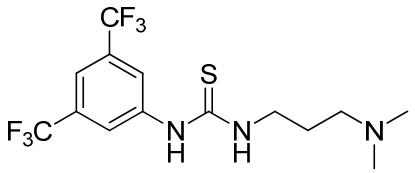
1d

1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-(dimethylamino)ethyl)thiourea 1d.[40] To a solution of 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (0.5 ml, 2.74 mmol, 1.0 eq) in ethyl acetate (30 ml) was added N,N-Dimethylethylenediamine (0.33 ml, 3.01 mmol,1.1 eq). The reaction was stirred at room temperature for 24 hours and then concentrated *in vacuo.* The crude product was then recrystallized from 10% ethyl acetate/ hexanes and washed with cold hexanes to yield **1d** (0.892 g, 91%) as white fluffy crystals. Mp 143-145ºC. ^{1}H NMR: (600 MHz, CD_3OD) δ8.21 (s, 2H), 7.62 (s, 1H), 3.76 (bs, 2H), 2.62 (t, J=6.48 Hz, 2H), 2.33 (s, 6H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 182.9, 143.2, 132.8 (q, J=33.30 Hz), 124.8 (q, J=271.83), 123.7, 117.8, 58.6, 45.5, 43.0 ppm. Anal. Calcd. for $C_{13}H_{15}F_6N_3S$: C: 43.45, H:4.21, N:11.69. Found C: 43.48, H: 4.09, N: 11.68.



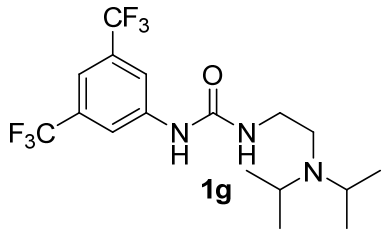
1e

1-(3,5-bis(trifluoromethyl)phenyl)-3-(3-(dimethylamino)propyl)urea 1e. To a solution of 3,5-bis(trifluomethyl) phenyl isocyanate (0.50 mL, 2.89 mmol, 1 eq) in ethyl acetate 30 mL was added 3-(Dimethylamino)-1-propylamine (0.40 mL, 3.18 mmol, 1.1 eq). The reaction was stirred at room temperature for 24 hours and then concentrated *in vacuo*. The crude product was then recrystallized from 10% ethyl aceate/90% hexanes and washed with cold hexanes to yield **1e** (0.965 g, 93%) as slightly yellow crystals. Mp 92-95ºC. ^{1}H NMR: (600 MHz, CD_3OD) δ 8.02 (s), 7.46 (s), 3.27 (t, J=6.84 Hz, 2H), 2.40 (t, J=7.62 Hz, 2H), 2.26 (s, 6H), 1.75 (m, J=7.23 Hz, 2H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ157.4, 143.5, 133.1 (q, J=33.02 Hz), 124.9 (q, J=271.80 Hz), 119.0, 115.4 (t, J=3.69 Hz), 58.1, 45.5, 39.2, 28.7 ppm. Anal. Calcd. for $C_{14}H_{17}F_6N_3O$: C: 47.06, H: 4.80, N: 11.76. Found C: 47.32, H: 4.77, N: 11.78.



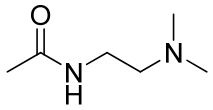
1f

1-(3,5-bis(trifluoromethyl)phenyl)-3-(3-(dimethylamino)propyl)urea 1f.[40] To a solution of 3,5-bis(trifluomethyl) phenyl isothiocyanate (0.5 mL, 2.74 mmol, 1 eq) in ethyl acetate 27 mL was added 3-(Dimethylamino)-1-propylamine (0.380 mL, 3.01 mmol, 1.1 eq). The reaction was stirred at room temperature for 24 hours and then concentrated *in vacuo.* Initially the product was chromatographed with 10% MeOH/CH_2Cl_2 to give an oil that solidified upon standing. Later, it was found that the crude product could also be recrystallized from diethyl ether/pentane and washed with cold pentane. A seed crystal could be added to aid in crystallization to yield **1f** (670.9 mg, 66%) as white crystals. Mp 83-86ºC. ^{1}H NMR: (600 MHz, CD_3OD) δ 8.19 (s, 2H), 7.66 (s, 1H), 3.66 (bs, 2H), 2.44 (t, J=7.44Hz, 2H), 2.27 (s, 6H), 1.86 (m, J=7.20Hz, 2H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 182.9, 143.2, 132.8 (q, J=33.35 Hz), 124.8 (q, J=271.79 Hz), 124.0 (m), 118.0, 58.3, 45.4, 44.0, 27.5 ppm. Anal. Calcd. for $C_{14}H_{17}F_6N_3S$: C:45.04; H:4.59, N: 11.25. Found C: 45.11, H: 4.54, N:11.32.



1g

1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-(diisopropylamino)ethyl)urea 1g. To a solution of 3,5-Bis(trifluromethyl)phenyl isocyanate (0.5 ml, 2.90 mmol, 1 eq) in ethyl acetate (30 ml) was added N,N-Diisopropylethylenediamine (0.56 ml, 3.19 mmol, 1.1 eq) The reaction was stirred at room temperature for 24 hours and then concentrated *in vacuo.* The crude product was then recrystallized from 3% ethyl acetate/hexane and washed with cold hexanes to yield **1g** (0.9146 g, 79% yield) as white crystals. Mp 152-154ºC ^{1}H NMR: (600 MHz, CD_3OD) δ 8.03 (s, 2H), 7.50 (s, 1H), 3.24 (t, J=6.81 Hz, 2H), 3.09 (m, J=6.56 Hz, 2H), 2.65 (t, J=6.81 Hz, 2H), 1.09 (d, J=6.54 Hz, 12H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 157.5, 143.6, 133.2 (t, J=49.52 Hz), 124.9 (q, J=271.65 Hz), 118.9, 115.4, 50.0, 45.7, 41.2, 20.9 ppm. Anal. Calcd. for $C_{17}H_{23}F_6N_3O$: C: 51.13, H: 5.80, N:10.52. Found C: 51.34, H:5.78, N:10.52.



9

N-(2-(dimethylamino)ethyl)acetamide 9. Following literature method with minor modifications.[41] To a solution fo triethylamine (1.4 mL, 0.11mmol, 1.1 eq) in dichloromethane (20 mL) cooled to 0ºC was added N,N-Dimethylethylenediamine (1 mL, 9.19 mmol, 1.0 eq). Then acetyl chloride (0.682 mL, 9.59 mmol, 1.0 eq) was added dropwise over the course of 15 min by syringe pump. The reaction was allowed to warm up to room temperature and stirred for ~3hrs. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted 3X with CH_2Cl_2. The organic layer was dried with $MgSO_4$, and concentrated *in vacuo*. The product was chromatographed (silica gel, 10% MeOH/CH_2Cl_2) to afford **9** as a light yellow oil (120.8 mg, 10%). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 6.08 (brs, 1H), 3.33 (q, J=5.6 Hz, 2H), 2.42 (t, J=5.9 Hz, 2H), 2.24 (s, 6H), 1.99 (s, 3H) ppm.^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 57.8, 45.1, 36.8, 23.3 The proton and carbon spectral data were in accordance with those described in the literature.[41]

2.2 Proline Derivative Preparation

General Procedure:[42]

Trans-4-hydroxy-L-proline (787 mg, 6 mmol, 1 eq) was placed in a round bottom and acetonitrile (10 mL) was added. The appropriate silane (21 mmol, 3.5 eq) was added. The reaction was cooled to 0ºC and DBU (22.2 mmol, 3.7 eq) was added. The reaction was allowed to warm to room temperature and stirred for 24 hours. The reaction was then quenched with pentane and the actonitrile layer washed with pentane 3x. The pentane extracts were combined and concentrated. Methanol (32 mL), THF (16 mL), water (16 mL), 2N NaOH (24mL) was added to the resulting oil and allowed to stir at room temperature for 90 minutes. The solution was then titrated to a pH of 6 with 1M HCl. The solvents were then removed under reduced pressure and the appropriate workup and crystallization procedure (shown below) was used.

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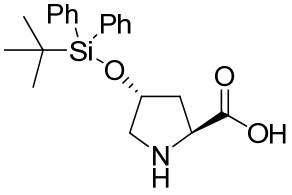
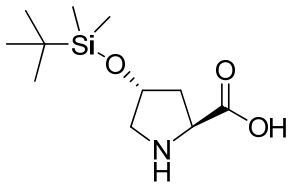


2a

(2S,4R)-4-(tert-butyldiphenylsilyloxy)pyrrolidine-2-carboxylic acid 2a.[43] Following general procedure. The organic solvents were removed under reduced pressure. To the resulting clear water layer, diethyl ether was added in ~1:1 diethyl ether:water ratio. Crystals should then form on the interface of the water diethyl ether layer. Crystals are then filtered and washed with cold diethyl ether to afford white crystals (1.65 g, 75%

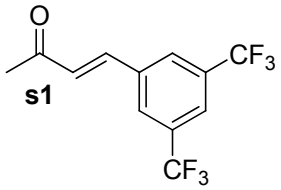
yield). ^{1}H NMR: (600 MHz, CD_3OD) δ 7.68-7.59 (m, 4H), 7.49-7.36 (m, 6H), 4.57 (bs, 1H), 4.25 (dd, J=7.56, 10.32 Hz, 1H), 3.30 (dd, J=4.04, 12.32 Hz, 1H), 3.19 (d, J=12.30 Hz, 1H), 2.33 (tdd, J=1.84, 7.54, 13.59 Hz, 1H), 1.92 (ddd, J=3.93, 10.20, 13.80 Hz, 1H), 1.07 (s, 9H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ 173.7, 136.97, 136.95, 134.2, 134.1, 131.5, 129.2, 74.2, 61.8, 54.7, 39.9, 27.5, 20.0 ppm. The proton spectrum closely resemble that in the literature, but updated splittings are provided.[43]



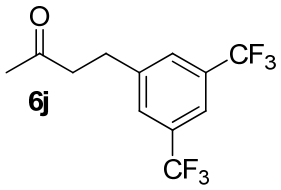
2e

(**2S,4R)-4-(tert-butyldimethylsilyloxy)pyrrolidine-2-carboxylic acid 2e.**[43] Following general procedure using 2.358 g of trans-4-hydroxy-L-proline. The solvents are removed under reduced pressure with heating to 40ºC until a white precipitate just begins to form. At this point water was added until all the precipitate goes into solution. The solution was then allowed to sit until crystals form. The crystals were filtered and washed with diethyl ether to afford white crystals (3.08 g, 70% yield). ^{1}H NMR: (600 MHz, CD_3OD) δ 4.66 (m, 1H), 4.19 (dd, J=7.59, 10.41 Hz, 1H), 3.44 (dd, J=3.78, 12.12 Hz, 1H), 3.18 (td, J=1.65, 12.12 Hz, 1H), 2.34 (tdd, J=1.91, 7.55, 13.52 Hz, 1H), 2.09 (ddd, J=3.78, 10.20, 13.74 Hz, 1H), 0.93 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ 174.0, 73.3, 61.7, 55.1, 40.2, 26.3, 19.0, -4.7, -4.8 ppm. The proton is in accordance with that described in the literature.[43]

2.3 Starting Material Synthesis



(3,5-bis(trifluoromethyl)phenyl)but-3-en-2-one s1.[44] A solution of 3,5-bis(trifluoromethyl)benzaldehyde (4 ml, 22.06 mmol, 1.1 eq) and 1-(Triphenylphosphoranylidene)-2-propanone (7.02 g, 22.06 mmol, 1.0 eq) in chloroform (110 ml) was heated to reflux for 4 hours. The mixture was cooled to room temperature, silica gel was added and the solvent was concentrated *in vacuo*. The resulting powder was purified by column chromatography on silica gel with 5% Ethyl Aceate/Hexanes to afford **s1** (6.18 g, 99% yield). Mp 48.5-50ºC. ^{1}H NMR: (600 MHz, $CDCl_3$) 7.97 (s, 2H), 7.89 (s, 1H), 7.55 (d, J=16.26 Hz, 1H), 6.84 (d, J=16.32 Hz, 1H), 2.43 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) 197.1, 139.3, 136.7, 132.6 (q, J=33.67 Hz), 130.0, 127.8, 123.5 (m), 123.0 (q, J=272.96 Hz), 28.1 ppm. HRMS (EI+): calcd for $C_{12}H_8F_6O$: 282.0479, found 282.0480.



4-(3,5-bis(trifluoromethyl)phenyl)butan-2-one 6j. Prepared following previously reported method[45]: A solution of Bis(cyclopentadienyl)titanium dichloride (0.262 g, 1.095 mmol, 0.05 eq), Triethylamine hydrochloride (15.07 g, 110 mmol, 5 eq), and zinc dust (3.58 g, 54.8 mmol, 2.5 eq) in dichloromethane (164 ml) was prepared and stirred

until the solution turned from red to green. A solution of **s1** (6.18 g, 21.90 mmol) in dichloromethane (274 ml) was added. The reaction was stirred for 24 hour. The reaction was quenched with NH_4Cl, then passed through celite and extracted with ether. The combined organic fractions were washed with brine and dried with $MgSO_4$ and concentrated. The residue was purified by krughror distillation at 50ºC under vacuum. Then the product was dissolved in CH_2Cl_2 and stirred with charcoal, passed through celite, evaporated and dried under vacuum to give **6j** as a slightly yellow colored oil (4.1g, 66% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.68 (s, 2H), 3.04 (t, J=7.38 Hz, 2H), 2.87 (t, J=7.38, 2H), 2.18 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) 206.2, 143.7, 131.6 (q, J=33.08 Hz), 128.6, 123.3 (q, J=272.49 Hz), 120.1 (m, J=3.80 Hz), 44.0, 29.7, 29.0 ppm. HRMS (EI+): calcd for $C_{12}H_{10}F_6O$: 284.0636, found 284.0631. Proton and carbon spectra were in accordance with those previously published for **6j**[46].

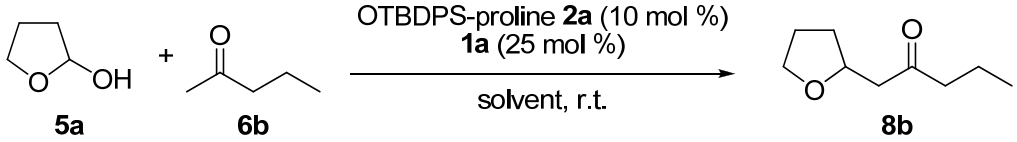
3. Screening Conditions

3.1 Solvent Screen

The proline derivative **2a** (11.1 mg) was weighed into 2mL vials. A 0.15 M stock solution of urea catalyst **1a** (25.7 mg, 75 μmol, 0.25 eq) was prepared in chloroform and 500 μL was dispensed into the vials. Solvent was evaporated overnight at 30ºC followed by drying under vacuum. A stock solution of starting materials 2-hydroxytetrahydrofuran (0.306 M), and methyl propyl ketone (1.53 M) was prepared in each solvent using a density of 1.084 g/mL for 2-hydroxytetrahydrofuran. A stock solution of mesitylene (0.100 M) was also prepared in each solvent. 220 μL of each respective solvent was

added to the vials, followed by 300 μL of the mesitylene stock. The reactions were initiated with 980 μL of the starting material stock. The reactions were stirred at room temperature, monitored by GC and yields were calculated from a calibration curve of product with reference to the mesitylene internal standard. After 24 hours, an aliquot (amount depended on the yield of the reaction) was removed and diluted into ~200 μL dichloromethane and the enantioselectivity analyzed by chiral GC.

Table 2.6: Solvent Screen



Entry	Solvent	Yield (%)[a]	ee (%)[b]	Time (hrs)
1	MeOH	82	-5	15
2	DMF	74	-2	13
3	MeCN	84	4	12
4	1,4 dioxane	82	11	8
5	$CHCl_3$	41	57	25
6	CH_2Cl_2	66	47	24

[a]Determined by GC analysis using mesitylene as an internal standard.
[b]Determined by chrial GC analysis of crude reaction mixture at 24 hours.

3.2 Proline Derivative Screen

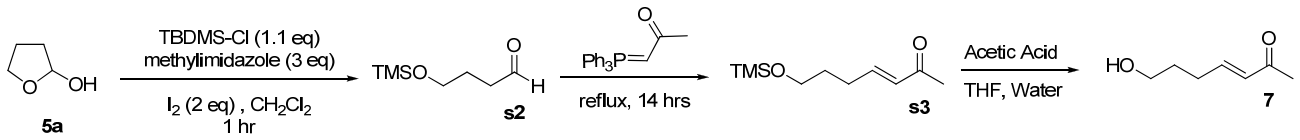
Each proline derivative (30.0 μmol, 0.10 eq) and urea catalyst **1a** (25.7 mg, 75 μmol, 0.25 eq) was weighed into 2mL vials. The reactions were initiated with 1500 μL of a stock solution containing: 2-hydroxytetrahydrofuran (300 μmol, 1500 μL, 0.20M, 1 eq), methyl propyl ketone (1500 μmol, 1500 μL, 1M, 5 eq), and mesitylene (30.0 μmol, 1500 μL, 0.02M, 0.10 eq). The reactions were stirred at room temperature, monitored by GC, and yields were calculated from a calibration curve of pure product in reference to the mesitylene internal standard. Upon deeming the reaction complete, an aliquot (amount depended on the yield of the reaction) was removed and diluted into ~200 μL dichloromethane and the enantioselectivity analyzed by chiral GC.

3.3 Amine/Urea/thiourea Additive Screen

Proline derivative **2a** (11.1 mg, 30.0 μmol, 0.10 eq) and urea/amine/additive catalysts (75 μmol, 0.25 eq) were weighed directly into 2mL vials. The reactions were initiated with 1500 μL of a stock solution containing: 2-hydroxytetrahydrofuran (300 μmol, 1500 μL, 0.20 M, 1 eq), methyl propyl ketone (1500 μmol, 1500 μL, 1M, 5 eq), and mesitylene (30.0 μmol, 1500 μL, 0.02 M, 0.10 eq). The reactions were stirred at room temperature, monitored by GC, and yields were calculated from a calibration curve of pure product in reference to the mesitylene internal standard. Upon the reaction deemed complete, an aliquot (amount depended on the yield of the reaction) was removed and diluted into ~200 μL dichloromethane and the enantioselectivity analyzed by chiral GC.

4. Mechanism and selectivity experiments

4.1 Synthesis of suggested enone intermediate



*4.1a Synthesis of 4-(t-butyl-dimethylsilyloxy)butyraldehyde **s2***

Following a previously reported method[47]: A stirred solution of **5a** (1.0 g, 11.35 mmol, 1 eq), methylimidazole (2.7 mL, 34.1 mmol, 3 eq) and iodine (5.76 g, 22.70 mmol, 2 eq) in dichloromethane (30 mL) was prepared. *tert*-butyldimethylsilyl chloride (1.882 g, 12.49 mmol, 1.1 eq) was then added and the reaction allowed to stir for 1 hour. The solvent was then concentrated. The residue was dissolved in ethyl acetate and washed with saturated aq $Na_2S_2O_3$ until the color went from orange to clear, indicating all the iodine was quenched. The organic phase was dried over $MgSO_4$ and concentrated. The product was purified by column chromatography 2% ethyl acetate/hexane to provide (0.9264 g, 40%) ^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.75 (t, J=1.71 Hz, 1H), 3.61 (t, J=5.97 Hz, 2H), 2.46 (dt, J=1.74, 3.54 Hz, 2H), 1.82 (m, 2H), 0.84 (s, 9H), 0 (s, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.5, 62.1, 40.8, 25.9, 25.5, 18.3, -5.4 ppm. Proton and carbon spectra match previously published spectra.[48]

*4.1b Synthesis of 7-(t-butyl-dimethylsilyloxy)butyraldehyde **s3***

A solution of **s2** (0.9264 g, 4.58 mmol, 1.1 eq) and 1-(Triphenylphosphoranylidene)-2-propanone (1.32 g, 4.16 mmol, 1 eq) in 20 mL $CHCl_3$ was prepared. The reaction was allowed to stir at reflux for 15 hours. The reaction was cooled and silica gel was added to the reaction mixture. The solvent was then concentrated and the powder directly

chromatographed with 5% EtOAc/Hexanes to yield (570.6 mg, 57% yield). ^{1}H NMR (600, $DDCl_3$) δ 6.78 (td, J=6.87, 15.96 Hz, 1H), 6.04 (td, J=1.50, 15.96 Hz, 1H), 3.59 (t, J=6.15 Hz, 2H), 2.25 (dq, J=1.40, 2.25 Hz, 2H), 2.19 (s, 3H), 1.64 (m, J=6.87 Hz, 2H), 0.85 (s, 9H), 0 (s, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.5, 148.1, 131.4, 62.2, 31.2, 29.0, 26.8, 25.9, 18.3, -5.4 ppm. Proton spectrum matched previously published spectrum.[44]

4.1c Synthesis of 7-hydroxy-3-heptene-2-one 7

Following previously reported method[49]: A solution of acetic acid (7.7 mL), water (3.9 mL), and THF (3.9 mL) was prepared and added to **s3** (554.2 mg, 2.103 mmol). The reaction was allowed to stir at room temperature for 2 hours. Longer stirring times resulted in the formation of cyclized product **8a**. At the end of 2 hours, diethyl ether was added and a saturated aqueous solution of Na_2CO_3 was added to neutralize the reaction. The organic layer was then washed 2x with saturated aqueous solution of Na_2CO_3 followed by 1x with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried with $MgSO_4$ and concentrated. The product was purified by column chromatography using 70% EtOAc/hexane to give alcohol **7** as an oil (18.3 mg, 7% yield). ^{1}H NMR (600, $DDCl_3$) δ 6.84 (td, J=6.87, 15.96 Hz, 1H), 6.11 (td, J=1.50, 15.96 Hz, 1H), 3.69 (t, J=6.41 Hz, 2H), 2.35 (m, 2H), 2.25 (s, 3H), 1.75 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.7, 147.7, 131.5, 61.9, 31.0, 28.8, 26.9, 26.9 ppm. The coupling constants are consistent with those expected for a *trans* product. The proton spectrum matched the corresponding peaks in the previously reported spectrum.[49]

4.2 Exposure of Suggested Enone Intermediate to Reaction Conditions

Proline derivative **2a** (1.8 mg, 4.80 μmol, 0.10 eq) and/or urea **1a** (4.12 mg, 12.0 μmol, 0.25 eq) were weighed directly into 2mL GC vials containing 250 μL inserts. The reactions were initiated with 240 μL of a stock solution containing: enone **7** (240 μL, 48 μmol of 0.2M solution in CH_2Cl_2) and mesitylene (240 μL, 4.80 μmol of 0.02 M solution in CH_2Cl_2). The reactions were stirred at room temperature and monitored by GC.

4.3 Plot of Reaction Progress and Decay of Enantioselectivity During Reaction

*4.3a Proline derivative **2e** – 10 mol %*

Proline derivative **2e** (7.4 mg, 30.0 μmol, 0.05 eq) and urea **1a** (25.7 mg, 75 μmol, 0.25 eq) were weighed directly into 2mL vials. The reaction was initiated with 1500 μL of a stock solution containing: 2-hydroxytetrahydrofuran (300 μmol, 1500 μL, 0.20M, 1 eq), methyl propyl ketone (1500 μmol, 1500 μL, 1M, 5 eq), and mesitylene (30.0 μmol, 1500 μL, 0.02M, 0.10 eq). The reactions were stirred at room temperature, monitored by GC for yield and enantioselectivity directly. The split ratio and sample size were changed during the course of the reaction in order to get an adequate response.

*4.3b Proline derivative **2a** – 10 mol %*

Proline derivative **2a** (11.1 mg, 30.0 μmol, 0.10 eq) and urea **1a** (25.7 mg, 75 μmol, 0.25 eq) were weighed directly into 2mL vials. The reaction was initiated with 1500 μL of a stock solution containing: 2-hydroxytetrahydrofuran (300 μmol, 1500 μL, 0.20M, 1 eq), methyl propyl ketone (1500 μmol, 1500 μL, 1M, 5 eq), and mesitylene (30.0 μmol, 1500 μL, 0.02 M, 0.10 eq). The reactions were stirred at room temperature, monitored by GC

for yield and enantioselectivity directly. The split ratio and sample size were changed during the course of the reaction in order to get an adequate response.

*4.3c Proline derivative **2a** – 5 mol %*

Proline derivative **2a** (67 mg, 0.180 mmol, 0.05 eq) and urea **1a** (309 mg, 0.900 mmol, 0.25 eq) were weighed directly into a 20mL vial. The reaction was initiated with 18 mL of a stock solution containing: 2-hydroxytetrahydrofuran (3.60 mmol, 18 mL, 0.20 M, 1 eq), methyl propyl ketone (18 mmol, 18 mL, 1M, 5 eq), and mesitylene (0.360 mmol, 18 mL, 0.02 M, 0.10 eq) in 1,4 dioxane. During the course of the reaction, aliquots of the reaction mixture (amounts varied to assure adequate sample for analysis) were removed and either directly analyzed or diluted into dichloromethane and enantioselectivities determined by chiral GC analysis. At ~7 hours an aliquot was removed, continuously stirred and directly analyzed for enantioselectivity by GC (adjusting the split ratio and sample size) for the remainder of the time.

4.4 Decay of Product Enantioselectivity Under Various Reaction Conditions

A series of reactions were set up containing various combinations of catalysts and reactants. The respective 2 mL vials were prepared with the following amounts of catalyst/starting materials: thiourea **1f** (28.0 mg, 75 μmol, 0.25 eq), proline derivative **2a** (11.1 mg, 30.0 μmol, 0.10 eq), and methyl propyl ketone (128 μL, 1200 μmol, 4 eq). The reactions were initiated with 1500 μL of a stock solution containing: product **8b** (300 μmol, 1500 μL, 0.20M, 1eq), and mesitylene (30.0 μmol, 1500 μL, 0.02 M, 0.10 eq) in 1,4 dioxane. After 36 hours the enantioselectivity of the reaction was assessed by withdrawing ~32 μL aliquots of the reaction mixture and diluting into ~200 μL

dichloromethane to give ~0.032M product concentration. Enantioselectivities were then determined by chiral GC analysis.

4.5 Nonlinear effect experiments

A series of reactions were set up containing various mole fractions of D-and L-proline (see below). Urea **1a** (171.6 mg, 0.5 mmol, 0.25 eq), was added to the vials. The reactions were initiated with 10 mL of a stock solution containing: 2-hydroxytetrahydrofuran (2 mmol, 10 mL, 0.20 M, 1 eq), methyl propyl ketone (10 mmol, 10 mL, 1M, 5 eq), and mesitylene (0.2 mmol, 10 mL, 0.02 M, 0.10 eq) in 1,4 dioxane. The reactions were vigorously stirred for 22 hours upon which an aliquot was removed, diluted into dichloromethane and analyzed for yield and enantiomeric excess by GC analysis.

Table 2.7: Amounts of D-and L-Proline Used

Entry	ee of proline (%)	D-proline (mg)	L-proline (mg)
1	100	0	23.1
2	80	2.3	20.6
3	60	4.6	18.4
4	40	6.9	16.2
5	20	9.2	13.8
6	0	11.5	11.5

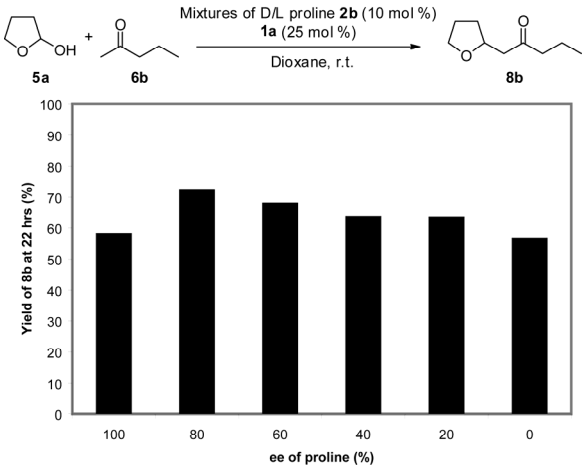
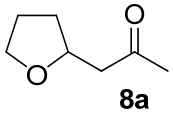


Figure 2.8: Yield of non-linear effect reactions at 22 hours.

5. Characterization of Products

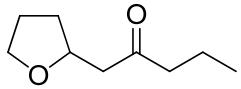
General Procedure: 2-hydroxytetrahydrofuran (1.14 mmol, 100 mg, 1 eq), was added to a 20mL vial and equipped with a stir bar. Dioxane (5.7 mL, 200 mM) was added. The appropriate ketone (5.68 mmol, 5 eq) is added. Proline derivative **2a** (0.114 mmol, 42.0 mg, 0.10 eq) and urea **1f** (0.284 mmol, 106 mg, 0.25 eq) are added. Upon complete consumption of starting material, as judged by GC analysis, silica gel was added to the reaction, solvent removed, and directly chomatographed using ethyl acetate/hexane mixtures to afford the desired compounds. Enatioselectivities were determined by chiral GC or HPLC analysis.



8a

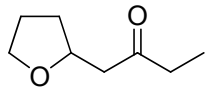
1-(tetrahydrofuran-2-yl)propan-2-one 8a: Prepared according to general procedure with dichloromethane as the solvent (due to high volatility of final product) using 113.0 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 4 hours. The product was

purified via flash chromatography on silica gel using 10% → 20% ethyl acetate/hexanes to give **8a** (65.9 mg, 40%) as a light yellow oil. R_f = 0.18 in 30% ethyl acetate/hexanes ^{1}H NMR: (600 MHz, $CDCl_3$) δ 4.22 (m, J=6.74 Hz, 1H), 3.86 (q, J=7.34 Hz, 1H), 3.73 (q, J=7.58, 1H), 2.75 (dd, J=7.29, 15.87 Hz, 1H), 2.56 (dd, J=5.55, 15.87 Hz, 1H), 2.19 (s, 3H), 2.10 (m, 1H), 1.89 (m, 2H), 1.47 (ddd, J=10.43, 5.99, 18.26 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $DCCl_3$) δ 207.2, 75.0, 67.8, 49.6, 31.5, 30.6, 25.5 ppm. HRMS (EI+): calcd for $C_7H_{12}O_2$: 128.0837, found 128.0831. The proton and carbon data were in accordance with those described in the literature.[50]



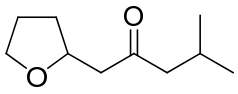
8b

1-(tetrahydrofuran-2-yl)pentan-2-one 8b: Prepared according to general procedure using 502.4 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 5 hours. The product was purified via flash chromatography on silica gel using 15% ethyl acetate/hexanes to give **8b** (719.8 mg, 81%) as a light yellow oil. R_f = 0.41 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ4.22 (m, J=6.77 Hz, 1H), 3.86 (dd, J=6.90, 15.06 Hz, 1H), 3.72 (dd, J=7.33, 14.99 Hz, 1H), 2.73 (dd, J=7.08, 15.78 Hz, 1H), 2.52 (dd, J=5.82, 15.78, 1H), 2.43 (dt, J=0.93, 7.37 Hz, 2H), 2.09 (td, J=6.07, 19.76 Hz, 1H), 1.93-1.85 (m, 2H), 1.61 (m, J=7.39 Hz, 2H), 1.46 (ddd, J=10.44, 6.00, 18.30 Hz, 1H), 0.92 (t, J=7.44 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ209.4, 75.1, 67.8, 48.6, 45.5, 31.5, 25.6, 17.0, 13.7 ppm. HRMS (ESI+): calcd for $[M+Na]^+$ $C_9H_{16}O_2Na$: 179.1043 Found 179.1046.



8c

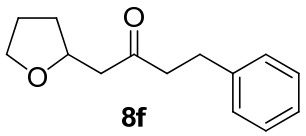
1-(tetrahydrofuran-2-yl)butan-2-one 8c: Prepared according to general procedure using 106.0 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 6 hours. The product was purified via flash chromatography on silica gel using 15% ethyl acetate/hexanes to give **8c** (133.0 mg, 78%) as an oil. R_f = 0.32 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ4.23 (m, J=6.75 Hz, 1H), 3.86 (q, J=7.32 Hz, 1H), 3.72 (q, J=7.44, 1H), 2.74 (dd, J=7.20, 15.72 Hz, 1H), 2.53 (dd, J=5.73, 15.69, 1H), 2.47 (dq, J=1.86, 2.42 Hz, 2H), 2.09 (m, 1H), 1.89 (m, 2H), 1.47 (ddd, J=10.47, 6.00, 18.27 Hz, 1H), 1.05 (t, J=7.29 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 75.2, 67.8, 48.3, 36.7, 31.5, 25.6, 7.6 ppm. HRMS (CI+): calcd for $C_8H_{15}O_2$: 143.1072, found 143.1070.



8d

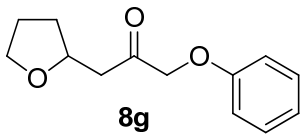
4-methyl-1-(tetrahydrofuran-2-yl)pentan-2-one 8d: Prepared according to general procedure using 100.0 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 8.5 hours. The product was purified via flash chromatography on silica gel using 10% ethyl acetate/hexanes to give **8d** (132.5 mg, 69%) as an oil. R_f = 0.44 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 4.22 (m, J=6.75 Hz, 1H), 3.85 (dd, J=7.32, 14.64 Hz, 1H), 3.72 (dd, J=7.41, 14.91 Hz, 1H), 2.73 (dd, 6.96, 15.90 Hz, 1H), 2.50 (dd, J=5.91, 15.87 Hz, 1H), 2.33 (d, J=7.08 Hz, 2H), 2.18-2.07 (m, J=6.67 Hz, 2H), 1.92-1.86 (m, 2H), 1.46 (ddd, J=10.14, 5.97, 18.30 Hz, 1H), 0.92 (d, J=6.66 Hz, 6H)

ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.1, 75.1, 67.8, 52.6, 49.1, 31.5, 25.6, 24.4, 22.6. 22.6 ppm. HRMS (CI+): calcd for $C_{10}H_{19}O_2$: 171.1385, found 171.1389.



8f

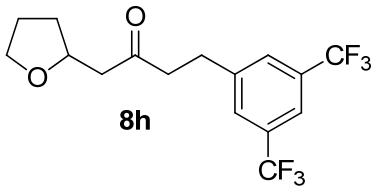
4-phenyl-1-(tetrahydrofuran-2-yl)butan-2-one 8f: Prepared according to general procedure using 111.5 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 5 hours. The product was purified via flash chromatography on silica gel using 2% →5% →10% → 20% ethyl acetate/hexanes to give **8f** (208.8 mg, 76%) as an oil. R_f = 0.38 in 30% ethyl acetate/hexanes. ^1H NMR: (600 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.19 (m, 3H), 4.21 (m, J=6.74 Hz, 1H), 3.84 (q, J=7.32 Hz, 1H), 3.71 (q, J=7.46 Hz, 1H), 2.90 (m, 2H), 2.79 (m, 2H), 2.72 (dd, J=7.23, 15.75 Hz, 1H), 2.51 (dd, J=5.61, 15.75 Hz, 1H), 2.07 (m, J=6.40 Hz, 1H), 1.88 (m, 2H), 1.44 (ddd, J=10.32, 5.97, 18.27 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ208.3, 141.1, 128.5, 128.3, 126.1, 75.1, 67.8, 48.9, 45.1, 31.5, 29.6. 25.6 ppm. HRMS (CI+): calcd for $C_{14}H_{19}O_2$: 219.1385, found 219.1386. The proton and carbon spectra matched those previously reported.[51]



8g

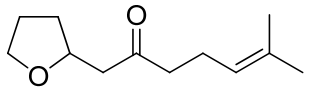
1-phenoxy-3-(tetrahydrofuran-2-yl)propan-2-one 8g: Prepared according to general procedure using 113.0 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 22 hours. The product was purified via flash chromatography on silica gel using a gradient

of 5 → 10 % ethyl acetate/hexanes to give **8g** (236.4 mg, 84%) as an oil. R_f = 0.33 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.99 (t, J=7.35 Hz 1H), 6.89 (d, J=8.58 Hz, 2H), 4.62 (q, J=14.54 Hz, 2H), 4.29 (m, J=6.86 Hz, 1H), 3.87 (q, J=7.34 Hz, 1H), 3.74 (q, J=7.44 Hz, 1H), 2.88 (dd, J=7.44, 15.84 Hz), 2.71 (dd, J=5.31, 15.87 Hz, 1H), 2.12 (m, J=6.45 Hz, 1H), 1.91 (m, 2H), 1.52 (ddd, J=10.41, 5.82, 18.12 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.8, 157.8, 129.6, 121.7, 114.6, 74.8, 73.2, 67.9, 45.2, 31.6, 25.5 ppm. HRMS (CI+): calcd for $C_{13}H_{17}O_3$: 221.1178, found 221.1163.



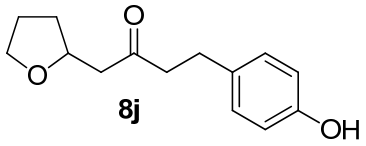
8h

4-(3,5-bis(trifluoromethyl)phenyl)-1-(tetrahydrofuran-2-yl)butan-2-one 8h: Prepared according to general procedure using 110.3 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 12 hours. The product was purified via flash chromatography on silica gel using a gradient of 5% → 20% ethyl acetate/hexanes to give **8h** (322.9 mg, 73%) as an oil. R_f = 0.41 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ7.71 (s, 1H), 7.65 (s, 2H), 4.20 (m, 1H), 3.84 (dd, J=6.81, 15.21, 1H), 3.72 (dd, J=7.62, 14.76 Hz, 1H), 3.09-3.00 (m, 2H), 2.93-2.82 (m, 2H), 2.70 (dd, J=7.86, 15.24, 1H), 2.55 (dd, J=4.95, 15.27 Hz, 1H), 2.07 (m, J=6.39 Hz, 1H), 1.92-1.85 (m, 2H), 1.46 (ddd, J=10.35, 6.03, 18.33 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ207.2, 143.6, 131.6 (q, J=33.06), 123.4 (q, J=272.56), 120.2 (m), 75.2, 67.9, 48.8, 44.0, 31.5, 28.9, 25.5 ppm. HRMS (CI+): calcd for $C_{16}H_{17}F_6O_2$: 355.1133, found 355.1117.



8i

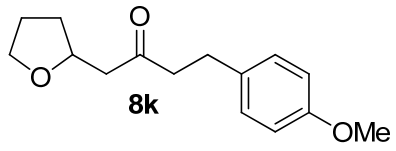
6-methyl-1-(tetrahydrofuran-2-yl)hept-5-en-2-one 8i: Prepared according to general procedure using 109.3 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 5 hours. The product was purified via flash chromatography on silica gel using a gradient of hexane, 2→10% ethyl acetate/hexanes to give **8i** (179.5 mg, 74%) as an oil. R_f = 0.48 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ5.06 (t, J=7.14, 1H), 4.22 (m, J=6.75 Hz, 1H), 3.85 (q, J=7.36 Hz, 1H), 3.72 (q, J=7.46 Hz, 1H), 2.73 (dd, J=7.02, 15.84 Hz, 1H), 2.52 (dd, J=5.76, 15.78 Hz, 1H), 2.48 (t, J=7.32 Hz, 2H), 2.25 (q, J=7.36 Hz, 2H), 2.09 (m, J=6.39, 1H), 1.89 (m, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.46 (ddd, J=10.37, 5.93, 18.32, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.1, 132.6, 122.8, 75.1, 67.8, 48.7, 43.6, 31.5, 25.6, 25.6, 22.3, 17.6 ppm. HRMS (ESI+): calcd for $C_{12}H_{20}O_2Na$ $[M+Na]^+$: 219.1356, found 219.1347.



8j

4-(4-hydroxyphenyl)-1-(tetrahydrofuran-2-yl)butan-2-one 8j: Prepared according to general procedure using 109.2 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 4.5 hours. The product was purified via flash chromatography on silica gel using a gradient of 15% → 20% → 25% ethyl acetate/hexanes to give **8j** (230.1 mg, 79%) as an oil. R_f = 0.12 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.02 (m, 2H),

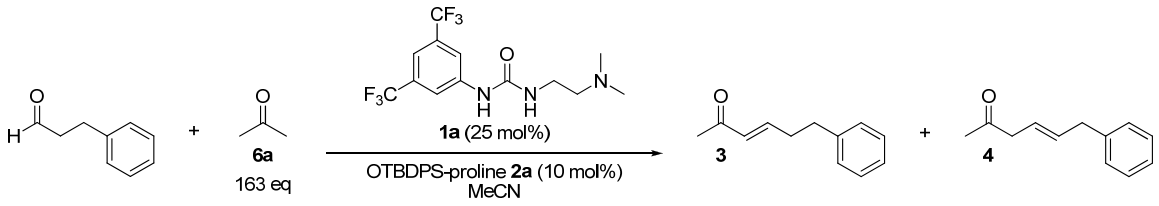
6.73 (m, 2H), 5.55 (s, 1H), 4.23 (m, J=6.84 Hz, 1H), 3.85 (m, 1H), 3.73 (m, 1H), 2.82 (m, 2H), 2.73 (m, 3H), 2.51 (dd, J=5.67, 15.81 Hz), 2.08 (m, 1H), 1.88 (m, 2H), 1.88 (m, 2.0H), 1.45 (ddd, J=10.40, 5.93, 18.26 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.8, 154.1, 132.9, 129.4, 115.3, 75.1, 67.8, 48.8, 45.3, 31.5, 28.7, 25.5 ppm. HRMS (CI+): calcd for $C_{14}H_{19}O_3$: 235.1334, found 235.1335.



8k

4-(4-methoxyphenyl)-1-(tetrahydrofuran-2-yl)butan-2-one 8k: Prepared according to general procedure using 102.5 mg 2-hydroxytetrahydrofuran. The reaction was stirred for 5 hours. The product was purified via flash chromatography on silica gel using 5% → 10% →20% ethyl acetate/hexanes to give **8k** (221.8 mg, 77%) as an oil. R_f = 0.29 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.10 (m, 2H), 6.82 (m, 2H), 4.21 (m, J=6.75 Hz, 1H), 3.78 (s, 3H), 3.71 (m, 1H), 2.84 (m, 2H), 2.73 (m, 3H), 2.50 (dd, J=5.61, 15.75 Hz, 1H), 2.07 (m, 1H), 1.88 (m, 2H), 1.44 (ddd, J=10.41, 6.03, 18.27 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.5, 158.0,133.1, 129.3, 113.9, 75.0, 67.8, 55.3, 48.9, 45.3, 31.5, 28.7, 25.6 ppm. HRMS (CI+): calcd for $C_{15}H_{21}O_3$: 249.1491, found 249.1493.

6. Aldol Reaction



6.1 Small scale reaction progress plot

Proline derivative **2a** (4.06 mg, 0.010 mmol, 0.10 eq) and urea **1a** (9.44 mg, 0.028 mmol, 0.25 eq) were weighed into a 2mL GC vial. Acetone (1.3 mL, 17.93 mmol, 163 eq) was added to the vial. The reaction was initiated with 220 μL of a stock solution containing 3-phenylpropionaldhyde (0.11 mmol, 220 μL, 0.05 M, 1 eq) and mesitylene as an internal standard (0.011 mmol, 220 μL, 0.05 M, 0.10 eq). The reactions were stirred at room temperature, and directly sampled by GC for reaction progress. Products and starting materials are referenced to mesitylene.

6.2 *Large scale aldol reaction*

Proline Derivative **2a** (35 mg, 0.094 mmol, 0.10 eq) and urea **1a** (81 mg, 0.235 mmol, 0.25 eq) were placed into a flask. Acetonitrile (1.9 mL) was added followed by acetone (11.2 mL, 153 mmol, 163 eq). The reaction was initiated with 3-phenylpropionaldehyde (0.125 mL, 0.941 mmol, 1 eq). The reaction was stirred at room temperature for 16 hrs. The reaction was then concentrated with silica gel and directly chromatographed using 2% diethyl ether/hexanes to afford the two observed products as light yellow oils.

Data for α,β product 3: (37.5 mg, 92% purity assuming *t*-butyldiphenylsilanol as an impurity based upon comparison to previously reported spectrum[52], 21% yield): ^{1}H NMR: (600 MHz, $CDCl_3$) δ7.31-7.27 (m, 2H), 7.22-7.16 (m, 3H), 6.81 (dt, J=6.81, 15.96

Hz, 1H), 6.09 (dt, J=1.50, 15.96 Hz, 1H), 2.79 (t, J=7.74 Hz, 2H), 2.58-2.51 (m, 2H), 2.22 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ198.5, 147.0, 140.7, 131.7, 128.5, 128.3, 126.2, 34.4, 34.1, 26.9 ppm. The proton and carbon data is in accordance with that reported in the literature.[53]

Data for β,γ product 4: (36.4 mg, 22% yield). Exists as a ~1:4.3 (*cis*:*trans*) mixture as judged by the peaks at 3.15 and 3.29 ppm. NMR data for the trans isomer is: ^{1}H NMR: (600 MHz, $CDCl_3$) δ7.31-7.26 (m, 2H), 7.22-7.15 (m, 3H), 5.74-5.67 (m, 1H), 5.65-5.60 (m, 1H), 3.38 (d, J=6.78, 2H), 3.15 (d, J=6.66, 2H), 2.14 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.1, 140.1, 133.7, 128.52, 128.48, 126.1, 123.4, 47.4, 39.0, 29.44 ppm. The proton data is in accordance with that reported in the literature.[54]

See Appendix 1 for copies of GC/HPLC chromatograms and corresponding chiral methods as well as ^{1}H and ^{13}C NMR spectra.

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CHAPTER 3

Continuous Proline Catalysis via Leaching of Solid Proline

Preface

In addition to the McQuade group's interest in examining organocatalytic reactions, we also have an active flow chemistry division. The goal of the work in this chapter was to combine both of these interests by transitioning the urea accelerated, proline-catalyzed α-aminoxylation to a flow process. We directly used solid proline in our setup. We found that flowing a soluble precursor through a packed-bed of solid proline created a soluble catalytic intermediate that could be used in the downstream α-aminoxylation.

Abstract[*]

Herein, we demonstrate that a homogeneous catalyst can be prepared continuously via reaction with a packed-bed of catalyst precursor. Specifically, we perform continuous proline catalyzed α-aminoxylations using a packed-bed of L-proline. The system relies on a multi-step sequence where an aldehyde and thiourea additive are passed through a column of solid proline presumably forming a soluble oxazolidinone intermediate. This transports a catalytic amount of proline from the packed-bed into the reactor coil for subsequent combination with a solution of nitrosobenzene, affording the desired optically active α-aminooxy alcohol after reduction. To our knowledge, this is the first example where a homogeneous catalyst is produced continuously using a packed-

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bed. We predict that the method will not only be useful for other L-proline catalyzed reactions, but also foresee that it could be used to produce other catalytic species in flow.

Introduction

Continuous flow chemistry,[1-3] performed in small dimension tubing or channels, differs from batch chemistry in that mixing and heat transfer are significantly faster and can be precisely controlled. In addition, continuous technology enables the generation and immediate use of unstable or hazardous intermediates[4-9] as well as the combination of many reactions in series to achieve multi-step synthesis[9-13]. Despite the many favorable attributes of micro and mesoflow reactors, the continuous use of solids remains challenging. The introduction of solids to a flow reactor is particularly difficult as most pumps function poorly with even small particulates which in turn can result in channel clogging. Though, using solids in flow has been the topic of a number of recent papers, they have focused on overcoming the challenges associated with the introduction and suspension of solid reagents and starting materials[14-18]. An area that has received less attention is the continuous use of solid catalysts (and catalyst precursors) that only partially or slowly dissolve/react into solution. (See Figure 3.1 for a comparison of solid catalysts that are used in flow). Proline is an example of such a catalyst[19] (others include zero valent transition metals, many solid acid catalysts, and other secondary amine catalysts). Proline is often added to a reaction as a solid and only a few mole percent dissolves into solution at any given time. Since proline is fairly inexpensive, it is an attractive test catalyst for designing new methods to utilize solid catalysts/catalyst precursors in flow.

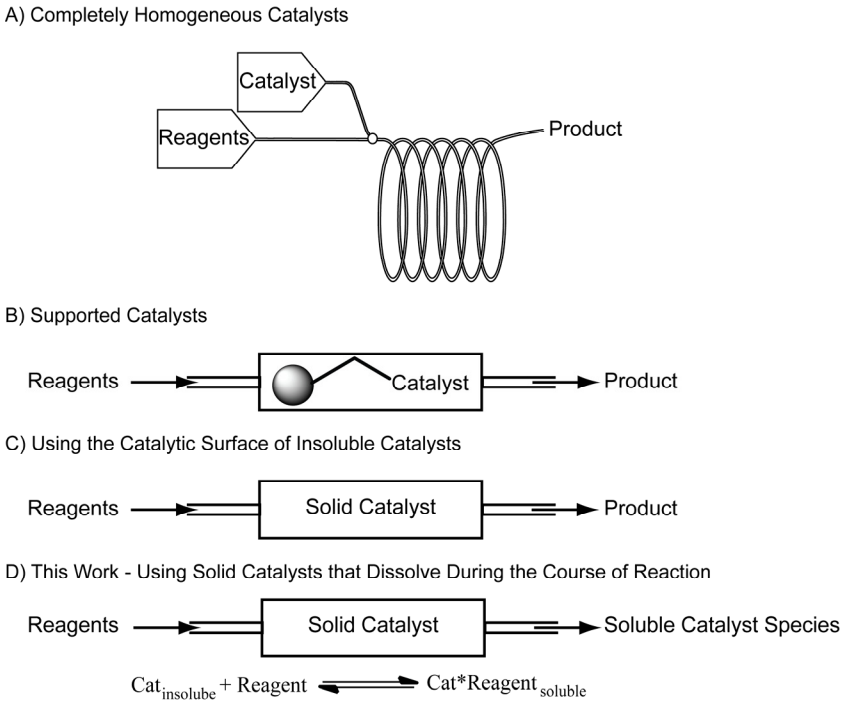


Figure 3.1: Methods for catalyst use in flow

Current strategies to use catalysts with limited solubility in flow rely on supporting them on resins or polymers (Figure 3.1A and B). This can be an attractive method as the catalysts are often easily recycled[20-24]. Finding a suitable solid support for a reaction, however, can prove time consuming and expensive. In addition, care must be taken to identify a support that provides both high activity for the catalyst and appropriate swelling properties to enable adequate mass transport (often the best solvent for the resin will not be the best for the reaction)[25-29]. With researchers becoming increasingly interested in developing continuous flow processes, the rapid assessment of catalyst conditions required for potential synthetic routes requires a simple approach to deal with limited solubility catalysts.

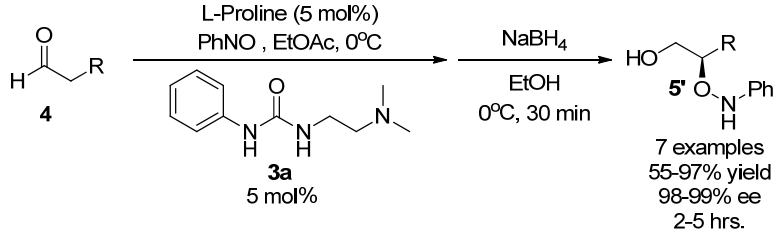
We have had both a long standing interest in the production, use, and management of solids[30-33] and reactions[34, 35] in flow as well as proline catalysis[36, 37]. This

prompted us to consider new strategies for implementing proline in a continuous system without resorting to proline analogs or tethered catalysts.[38-40] Achieving this goal would enable ourselves and others to perform proline-catalyzed reactions such as aldol,[41-43] Mannich[42], and α-aminoxylations, α-aminations, or α-halogenations[44] continuously.

We hypothesized that the proline-catalyzed α-aminoxylation could be implemented in flow with reasonably short residence times using a urea additive. Many researchers, including us[36, 37], have found that urea[45] additives increase the rate of various proline-catalyzed reactions[46-50]. The role that ureas play remains unclear and a number of hypotheses have been suggested. Initially, researchers gathered ^{1}H NMR, UV, and fluorescence data to show that ureas enhance the solubility of proline through a host-guest interaction between the urea and proline carboxylate – a substrate independent model[49, 50]. However, it has been proposed that substrate/urea/proline interactions may also contribute to the rate enhancement[50]. Our group observed that a urea tethered to a tertiary amine increases the rate of a number of batch reactions, including the α-aminoxylation reaction[36, 37]. For the α-aminoxylation reaction, we proposed that the urea promotes formation of the active enamine intermediate via breakdown of the putative oxazolidinone intermediate – a substrate dependent model. Here, we report that a packed-bed of solid proline can be used to create a homogeneous catalyst and we use this system to perform continuous α-aminoxylations. Not only do we illustrate a unique use of catalysts in flow, but we provide additional insight into the role of additives in proline-catalyzed reactions.

Results and Discussion

In our previously published batch work, we found that the combination of L-proline and bifunctional urea **3a** greatly accelerated the rate of α-aminoxylation (Scheme 3.1). It was shown that a longer linker between the urea and amine functionality enhanced the rate of reaction (see supporting information of reference 37). The rate enhancement enabled the reaction to be preformed in greener solvents such as ethyl acetate instead of the more commonly used chloroform. We have had a long standing interest in converting the reaction into a continuous process, but recognized that proline's solubility would hinder its use in flow. To circumvent this problem, we envisioned using a cartridge of solid proline as a pre-catalyst source whereby flowing a combination of solvents/reactants/cocatalysts through the packed-bed would produce the active, homogeneous, oxazolidinone catalyst.



Scheme 3.1: Prior results for batch α-aminoxylation reaction

To test our hypothesis, we used a Vapourtec R series reactor system[51] consisting of HPLC pumps for solvent and reagent inputs, a low temperature tube reactor containing a glass column packed with 1 gram of proline and a low temperature 10 mL PFA coil tube reactor where each reagent stream could be pre-cooled prior to mixing (Figure 3.2). As we demonstrate later, the success of our experiments depended on the ability of the system to heat/cool the packed-bed and the reaction coil independent of each other.

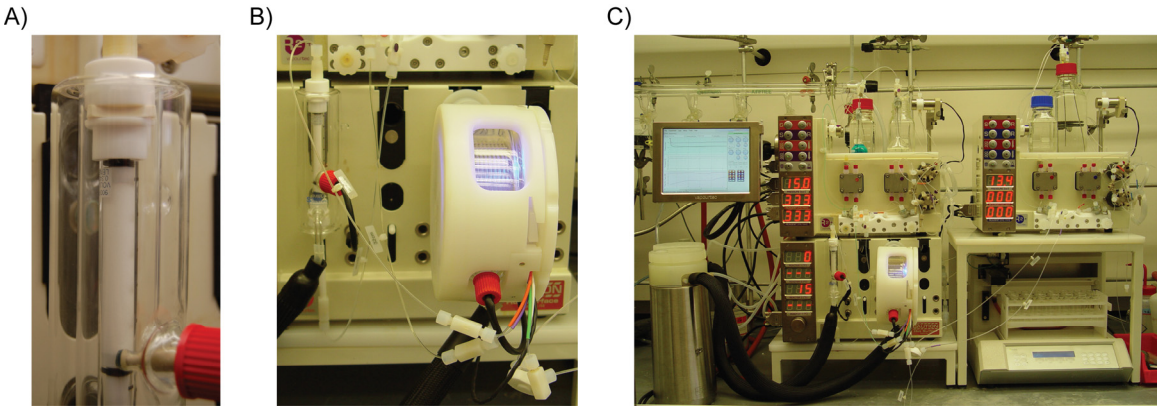


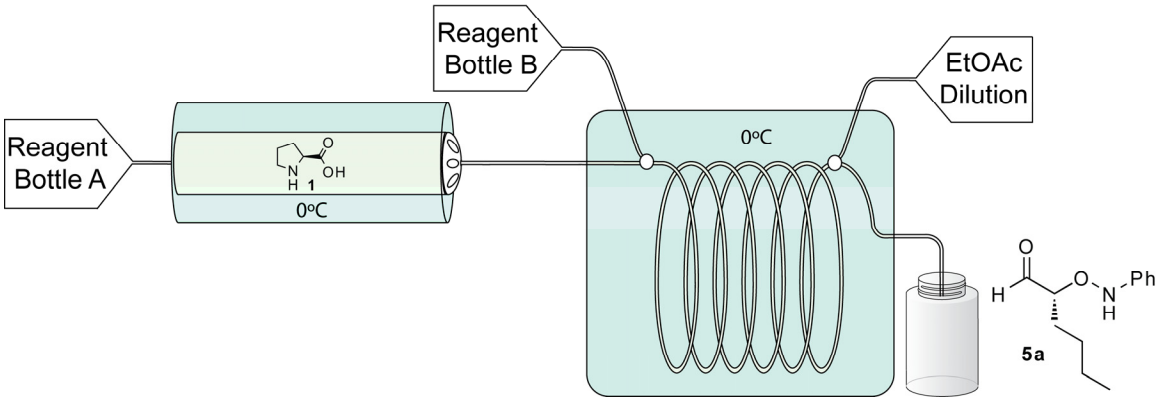
Figure 3.2: General reactor setup. A) A glass Omnifit column is packed with 1 gram of proline. B) The column is then placed in-line with a 10 mL PFA coil tube reactor. C) The components are connected to HPLC pumps for solvent and reagent inputs. The reactor is controlled by a computer to program the timing of reagent/solvent inputs and fraction collection.

Using this device configuration, reactions were performed to identify conditions that favored reaction between the aldehyde and proline packed-bed to yield enough soluble oxazolidinone catalyst to support rapid α-aminoxylations. We were particularly interested to address what substrate/additive components were necessary to dissolve the solid proline. Since the inherent solubility of proline in ethyl acetate is very low we extrapolated that solvent alone should be insufficient to dissolve enough catalytic proline[37,52]. Furthermore, we knew from our previous batch work that a urea additive would be beneficial to provide reaction rates suitable for use in flow[37].

Therefore, configurations varying a combination of reagents and catalysts entering the packed proline column were investigated. For our initial experiments we selected a 15 minute coil residence time and temperature of 0ºC for both the column and the coil based on our prior knowledge of the reaction in batch. We began by determining

the necessity of a urea cocatalyst. We were surprised to find that when hexanal alone was passed through the column and combined with nitrosobenzene in the coil the desired product was not detected by crude ^{1}H NMR analysis (Table 3.1, entry 1). This indicates that with this reactor setup, the reaction is too slow without a urea additive to be a viable method. Additionally, flowing thiourea **3b** (0.047 M in EtOAc) through the proline packed-bed prior to combination with the other reaction partners resulted in no detectable reaction (Table 3.1, entry 2). This shows that thiourea **3b** alone cannot solubilize enough proline to support the reaction. When hexanal alone, however, was passed through the column and combined with the remaining reagents (including thiourea **3b**) in the coil the reaction produced 27% yield and 99% ee (Table 3.1, entry 3). This indicates that the aldehyde alone can react with solid proline to produce a reactive homogeneous catalyst. However, when both thiourea **3b** and hexanal were used in the same stock solution and passed through the column the reaction had 43% yield with 98% ee (Table 3.1, entry 4). This increase in yield relative to when hexanal alone was passed through the column suggests that the rate of proline leaching is enhanced by the addition of thiourea **3b**. Consequently, it appears that our observed rate enhancements with thiourea **3b** cannot be attributed to a model involving only proline-urea interactions resulting in enhanced solubility and that urea/proline/substrate interactions are responsible for the observed reactivity using this combination of thiourea, substrate and proline.

Table 3.1: Screening of reactor setup

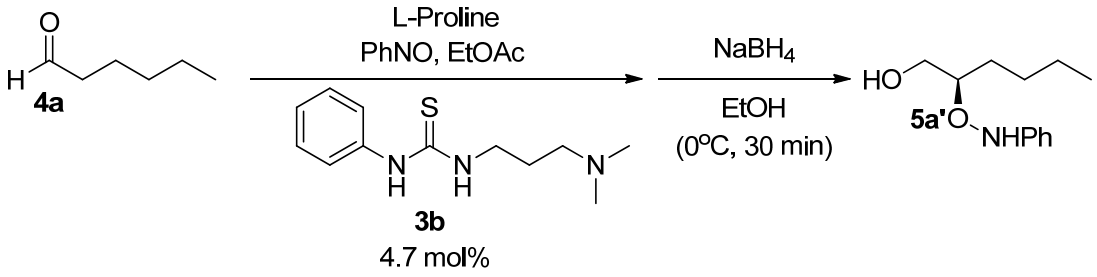


Entry	Reagent Bottle A	Reagent Bottle B[a]	Yield (%)	ee (%)[c]
1	Hexanal	Nitrosobenzene	NR[b]	NA
2	Thiourea **3b**	Nitrosobenzene + Hexanal	NR[b]	NA
3	Hexanal	Nitrosobenzene + Thiourea **3b**	27[d]	99
4	Hexanal + Thiourea **3b**	Nitrosobenzene	43[d]	98

[a] Entry 4 also contained dodecane as an internal standard. [b] NR = no reaction as determined by ^{1}H NMR analysis of the crude reaction mixture after reduction. [c] Determined by chiral HPLC. [d] Isolated yield (due to instability of the aldehyde, products were reduced in batch to their corresponding 2-aminooxy alcohols prior to isolation). NA = not applicable. See supporting information for detailed reaction conditions.

We were delighted to find that further increasing the residence time of the coil to 20 minutes with the same reagent configuration resulted in 69% yield (Table 3.2, entry 2). We therefore used a setup where a thiourea/aldehyde stock solution was passed through the proline packed bed before entering the coil and reacting with nitrosobenzene for further experiments.

Table 3.2: Screening of temperature and residence time



Entry	Column Temperature (°C)	Coil Temperature (°C)	Residence Time (minutes)	Yield (%)[a]	ee (%)[b]
1	0	0	15	43	98
2	0	0	20	69	98
3	0	15	15	82	98
4	0	15	20	85	98
5	0	15	10	61	98
6	0	10	20	84	98
7	0	5	20	86	98
8	0	5	25	81	98
9	-5	5	20	84	98
10	5	5	20	75	98
11	10	5	20	66	98
12	20	5	20	68	98

[a] Isolated yield (due to instability of the aldehyde, products were reduced in batch to their corresponding 2-aminooxy alcohols prior to isolation). [b] Determined by chiral HPLC. See supporting information for detailed reaction conditions.

As all of the reactions performed in Table 3.1 had the same residence time and temperature, yield can be used as a rough proxy for reaction rate. We conjecture, based on our prior work in the area, that the aldehyde slowly reacts with solid L-proline in the cartridge to form the soluble oxazolidinone intermediate (Figure 3.3, part C), leaching proline out of the column and into the coil for reaction with nitrosobenzene. The increased yield observed when both hexanal and thiourea **3b** were passed through the proline-bed suggests that more catalyst was drawn into solution resulting in a faster reaction rate. In our prior batch experiments, we proposed that the urea aided in the

breakdown of the oxazolidinone intermediate (Figure 3.3, part **C**) for rapid reaction with nitrosobenzene and this thesis is supported by our observations herein.

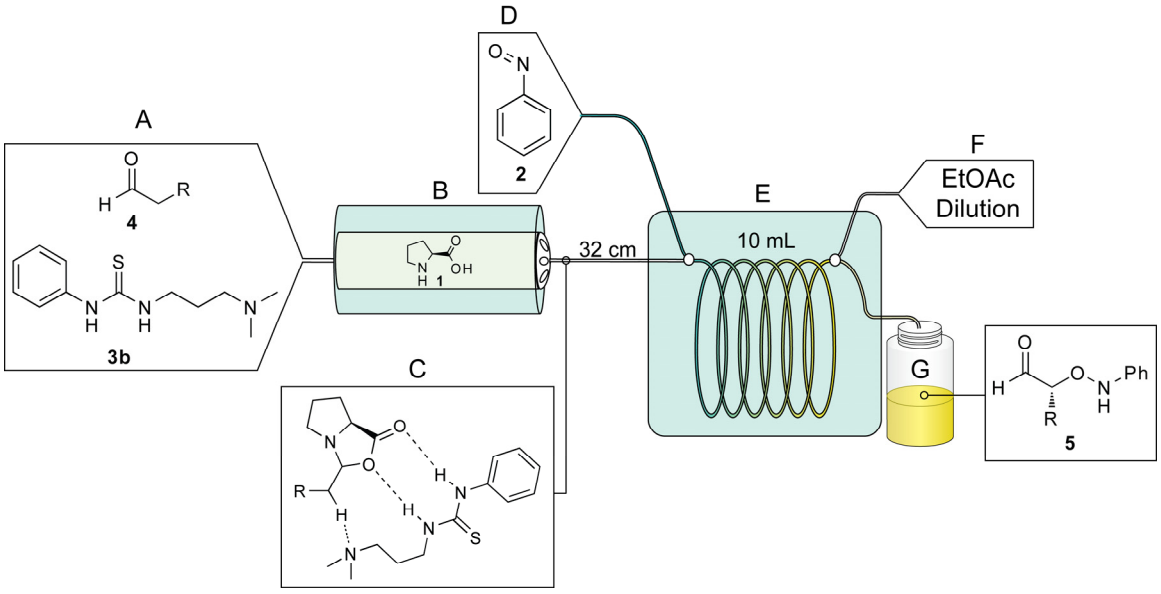


Figure 3.3: Schematic of the reactor setup. As the starting aldehyde and thiourea **3b** (A) enter the proline packed bed (B) an oxazolidinone intermediate is formed, drawing the proline into solution (C). Upon pre-cooling in reactor coil (E) the intermediate is mixed with nitrosobenzene (D). Prior to exiting, ethyl acetate is added to dilute the reaction (F) and product is collected into vials (G) for further reduction, work-up, and isolation.

With evidence for adequate proline transport into the coil, optimization experiments were performed. From previously published studies on the α-aminoxylation we believed that careful control of the temperature would be necessary to avoid the formation of byproducts and to realize high enantioselectivity. The forced convection cooling system, facilitated easy and precise temperature control of both the column and coil independently. Reported byproducts include the self-aldol product, the formation of azoxybenzene from the reaction of the desired product and nitrosobenzene and finally azobenzene via product disproportionation[53-55]. Side product suppression is both solvent

and temperature dependent. Hayashi reported that when the reaction is performed at room temperature in acetonitrile with 30 mol% proline the reaction is complete in 10 minutes, but has 29% yield[55]. MacMillan, however, found the reaction to be rapid in chloroform at room temperature with 78% yield using 10 mol% proline[56]. While our prior batch work using urea **3a** in ethyl acetate found that the α-aminoxylation of hexanal worked well at 0ºC with 5 mol% proline in 2 hours. Therefore, we studied the impact of both the packed-bed and reaction coil temperature on enantioselectivity and product yield.

To begin, we kept the column temperature at 0ºC and increased the *coil temperature* to 15ºC. Gratifyingly, a 15 minute residence time provided 82% yield (Table 3.2, entry 3). Increasing the residence time to 20 minutes provided little gain in yield, while reducing the residence time to 10 minutes provided only 61% yield (Table 3.2, entries 4 and 5). We found that as the coil temperature was decreased from 15ºC to 10ºC to 5ºC the yield for a 20 minute residence time remained steady (Table 3.2, entries 4, 6, and 7). A further reduction to 0ºC, however, showed a decrease to 69% (Table 3.2, entry 2). At each of these temperatures the enantioselectivity remained high.

Next, *packed-bed temperature* was varied to determine how temperature influenced the formation of the active catalyst species from hexanal, proline, and thiourea **3b**. We found that at column temperatures less than 0ºC the reaction performed well (Table 3.2, entries 7 and 9). As the temperature was increased to 5, 10, and 20ºC the yield dropped to 68% at 20ºC (Table 3.2, entries 10, 11, and 12). Therefore, for further experiments we chose a column temperature of 0ºC and coil temperature of 5ºC with a 20 minute residence time. It is clear, however, from the parameters investigated that when

simple sterically unencumbered aldehydes are used this reaction works well under a variety of conditions.

To assess the long term stability and activity of the L-proline packed bed, the system was run continuously for over 4 hours. After the system reached equilibrium, 20 mL fractions of product were periodically collected, reduced and purified. The data shown in Figure 4 indicate that the reaction is stable over this period of use. During the ~5 hr collection period, assuming an average yield of 78%, approximately 9.8 g is produced. The entire run passed 80 mL of hexanal/thiourea **3b** stock solution through the column. Upon completion of this study it was determined that 82% of the proline was consumed (823.1 mg out of 1 g) (Figure 3.4).

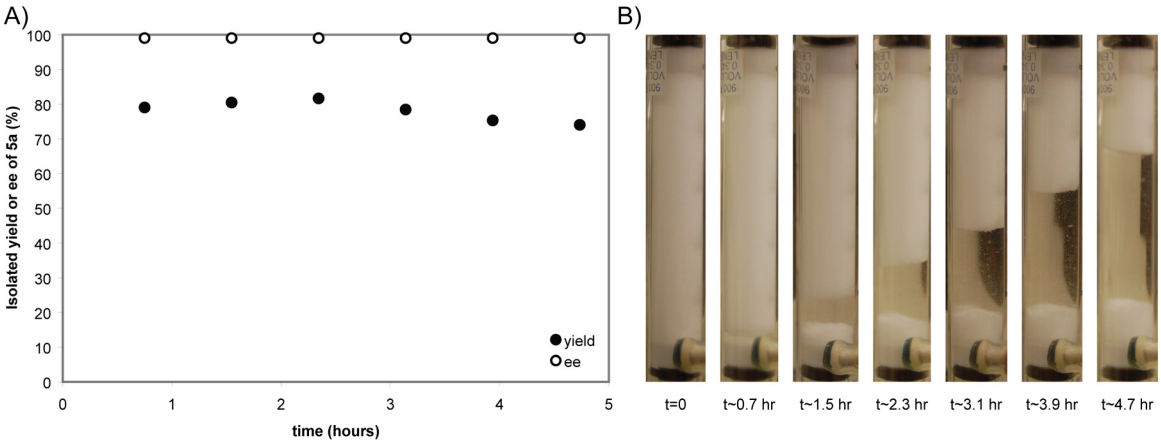
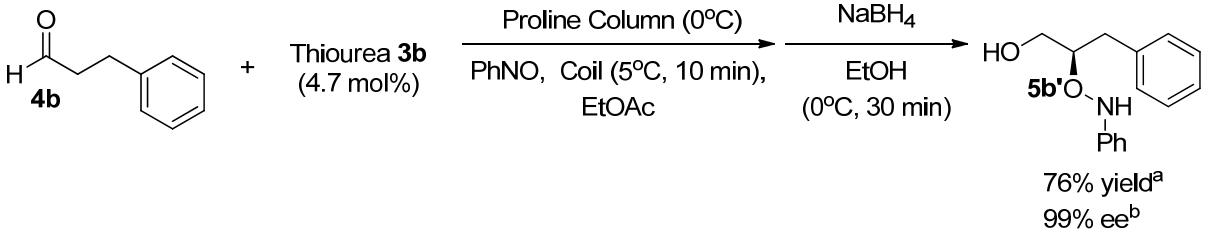


Figure 3.4: The long-term stability of a proline packed bed in the α-aminoxylation reaction of hexanal. A solution of hexanal (3 M in EtOAc) and thiourea **3b** (0.047 M in EtOAc) was passed through a packed-bed of proline (entering at the bottom of the column and exiting at the top) at 0ºC combined with a solution of nitrosobenzene (1 M in EtOAc) in a coil at 5ºC with a 20 minute residence time in the coil for over 4 h. A) 20 mL of product were periodically collected into vials, reduced in batch, and purified. The resulting yields and enantioselectivities were plotted as a function of time. B) Close up

images of the proline column (see figure 3.2A) showing the amount of proline consumed during the course of reaction.

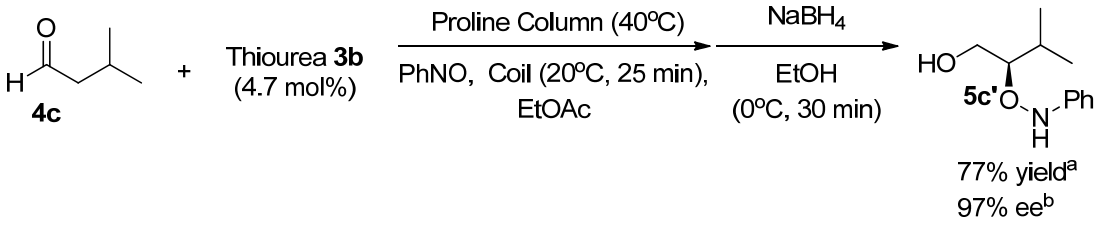
As further support that the direct use of solid catalysts in flow is a viable strategy, two additional substrates, 3-phenylpropionaldehyde and isovaleraldehyde, were selected because they have different properties compared to hexanal and we predicted that they would require alterations to the system to maximize yield. As a starting point, the conditions optimized for hexanal were investigated. With 3-phenylpropionaldehyde, the use of a 0ºC column temperature, 5ºC coil temperature and a 20 minute coil residence time led to rapid reaction (based upon color change in the coil) and subsequent reactor clogging. This led us to conclude that this aldehyde reacts rapidly with proline to yield an oxazolidinone with lower solubility than hexanal and that lowering the overall residence time would limit the amount of aldehyde reacting with proline. We found that our assertion was reasonable because reducing the residence time to 10 minutes provided 76% yield and 99% ee (Scheme 3.2).



Scheme 3.2: Reaction with 3-phenylpropionaldehyde through reactor setup. [a]Isolated yield, due to the instability of the aldehyde, the product was reduced in batch to the corresponding 2-aminoxy alcohol prior to isolation. [b]Determined by chiral HPLC.

When isovaleraldehyde was investigated at the optimized hexanal conditions, 0ºC column temperature, 5ºC coil temperature and a 20 minute coil residence time, there was

little conversion as judged by GC analysis. We were not surprised by this observation as increased steric hindrance about the aldehyde can suppress the rate of oxazolidinone formation. With limited proline (in the form of oxazolidinone) entering the system, the rate of α-aminoxylation decreases significantly. From our hexanal and 3-phenylpropionaldehyde experiments, we learned that by adjusting one of three parameters (residence time or coil/packed-bed temperature) we could improve the amount of catalyst entering the system. In this particular case, we predicted that unlike 3-phenylpropionaldehyde the isovaleraldehyde was forming the oxazolidinone slowly. Furthermore, we predicted that raising the packed-bed temperature would increase the rate of proline/isovaleraldehyde reaction resulting in more rapid formation of the soluble catalyst species. A quick survey of temperatures revealed that a 40ºC packed-bed temperature and a 20ºC coil temperature with a 25 minute residence time provided 76% yield and 97% ee (Scheme 3.3). It is apparent from these results and our initial conditions that substrate to substrate optimization can be rapidly achieved by a quick survey of the three critical parameters. The data further underscore the value of running reactions continuously.



Scheme 3.3: Reaction with isovaleraldehyde through reactor setup. [a]Isolated yield, due to the instability of the aldehyde, the product was reduced in batch to the corresponding 2-aminooxy alcohol prior to isolation. [b]Determined by chiral HPLC.

Conclusion

We have demonstrated that a packed-bed of proline can be used to continuously form a soluble catalyst through reaction with an aldehyde and co-catalytic urea. The formed soluble catalyst can support a variety of α-aminoxylation reactions with good yields and high enantioselectivities. The system is designed so that the first step flows aldehyde and urea solution through the proline packed-bed to generate the catalytic intermediate (presumably an oxazolidinone). This catalyst solution is then combined with a stream of nitrosobenenze resulting in the α-aminoxylation. The most critical parameters that control yield and selectivity were identified and these parameters were varied to optimize the system for each substrate. We predict that this basic setup can be adapted to generate a wide range of other catalysts by replacing proline with another solid catalyst precursor. We are currently investigating the combination of ligands and solid metal salts to generate transition metal catalysts continuously.

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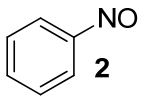
Experimental Section

1. General Information

Flash chromatography was performed using silica gel (230-400 mesh). For analytical thin layer chromatography (TLC), silca gel 60 F_{254} plates were used. All commercial reagents were used without further purification with the following exceptions: Hexanal, hydrocinnamaldehyde, and isovaleraldehyde were distilled prior to use. We found it helpful to filter the stock solutions of aldehyde, thiourea, and nitrosobenzene through fritted syringes and ethyl acetate with standard filter paper prior to use as this removed any fine particulates. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on 600 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), integration.

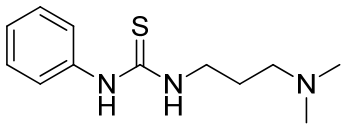
Reactions were performed with a commercially available Vapourtec R series reactor controlled by FlowCommander™ software. Solid proline catalyst was packed into a glass Omnifit column (6.6 mm diameter) fitted with Vapourtec end caps and sintered glass frits. All tubing and fittings were supplied with the reactor, but the tubing was standard 1.00 mm bore PFA and standard PTFE fittings.

2. Catalyst and Reactant Synthesis



2

Nitrosobenzene (2). Prepared according to previously reported method with some modifications.[57] A solution of sodium tungstate dihydrate (1.02 g, 3.08 mmol, 0.014 eq) in 20 mL hydrogen peroxide (30 wt. % in H_2O) was cooled to 15-19° C. Aniline (20 mL, 220 mmol, 1 eq) was added at a constant flow rate of 0.333 mL/min via syringe pump being sure to keep the temperature between 15-19°C. Throughout the course of the reaction, three 5 mL portions of hydrogen peroxide were added. Since the start of the aniline addition, the reaction stirred for 1.25 hours. The resulting solid was collected by vacuum filtration then stirred in 150 mL of water for 10 minutes to solubilize any residual catalyst. The solid was collected by vacuum filtration, rinsed with water and then cold ethanol. The solid was recrystallized from ethanol (0.1 g of solid to 1 mL of ethanol). The resulting crystals were collected and dried under vacuum over P_2O_5 for 24 hours to yield **2** (8.86 g, 38%) as white crystals with some residual water. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.90 (d, J=7.3 Hz, 2H), 7.71 (m, 1H), 7.62 (t, J=7.8 Hz, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.1, 135.7, 129.5 (2C), 121.1 (2C) ppm.



3b

1-(3-(dimethylamino)propyl)-3-phenylthiourea (3b). Phenyl isothiocyanate (5.0 mL, 41.9 mmol, 1 eq) and 3-(dimethylamino)-1-propylamine (5.8 mL, 46.0 mmol, 1.1 eq) were added to 460 mL of ethyl acetate. The reaction was stirred at room temperature for 17 hours and then concentrated *in vacuo*. The crude product was then recrystallized in 35% EtOAc/hexanes and washed with cold hexanes to yield **3b** (9.05 g, 91%) as white crystals. ^{1}H NMR: (600 MHz, CD_3OD) δ 7.39 (t, 2H, *J*=7.8 Hz), 7.29 (d, 2H, *J*=7.3 Hz), 7.23 (t, 1H, *J*=7.4 Hz), 3.62 (br s, 2H), 2.35 (t, 2H, *J*=6.9 Hz), 2.11 (s, 6H), 1.75 (m, 2H, *J*=6.9 Hz) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 182.1, 139.5, 130.6 (2C), 127.2, 126.3 (2C), 59.0, 45.5 (3C), 27.3 ppm. Anal. Calcd. For $C_{12}H_{19}N_3S$ C: 60.72, H: 8.07, N: 17.70, S: 13.51. Found C: 60.86, H: 8.01, N: 17.64, S: 13.22.

3. General Reactor Setup

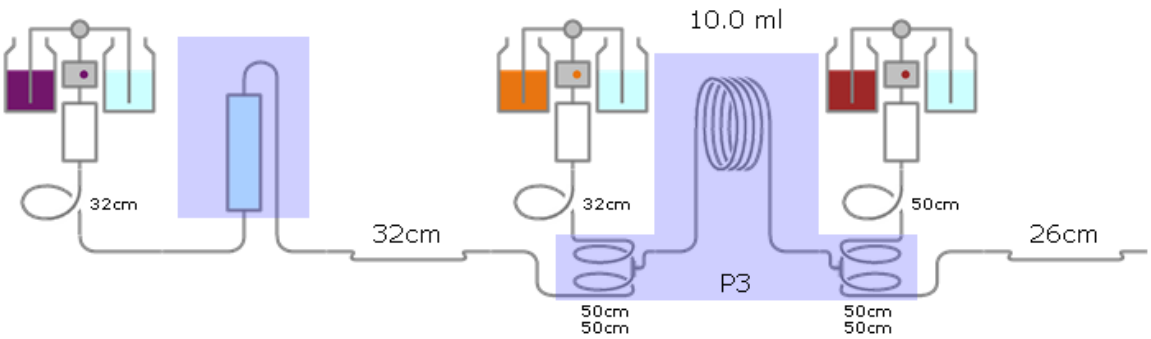


Figure 3.5: General reactor setup schematic

Description from left to right: The first pump was connected with 32 cm of drop tubing to a glass Omnifit column (6.6 mm diameter) containing 1.0 g of proline with a measured void volume ~1.4 mL. An additional 32 cm of tubing connected the column to a 10.0 mL tube reactor were reagents were pre-cooled prior to mixing (see below for dimensions). The second pump was also connected to an inlet of the tube reactor using 32 cm of drop tubing. The final pump(s), were connected to the "quench inlet" of the tube reactor with 50 cm of drop tubing. Depending on the residence time and total flow rate needed, 1-2 pumps were used, each with 50 cm of drop tubing. To accommodate two pumps, a t-mixer outside the tube reactor was used to generate a single stream of ethyl acetate. The dilution was used to slow the reaction before exiting the coil for collection using a fraction collector. Two 8 bar backpressure regulators (not shown) were connected in series along with additional tubing (not shown) to reach the fraction collector.

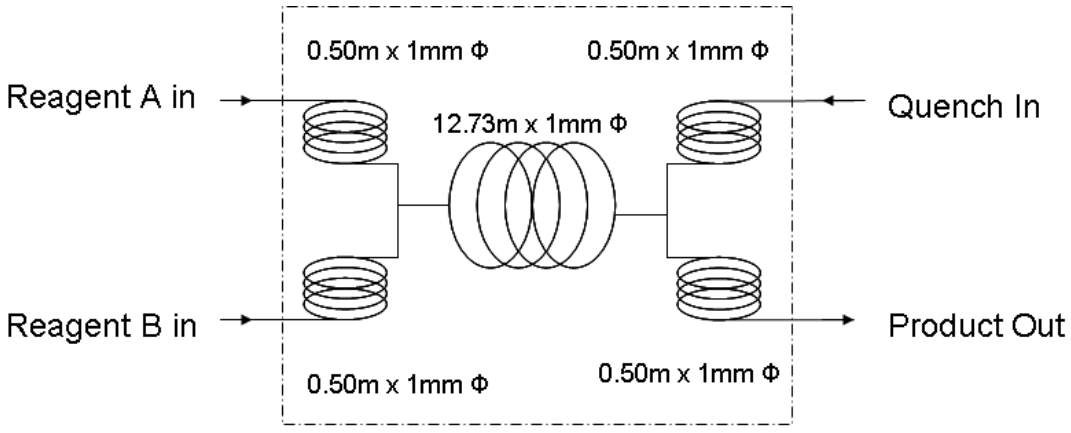


Figure 3.6: Detailed schematic of the 10.0 mL coil reactor

4. Experiments to assess reactor setup (Table 3.1)

A series of reactions were run to asses the best configuration for reactor operation. As a general setup, a glass Omnifit column (6.6 mm diameter) and a 10 mL reactor coil, each with independent temperature control were used. 1.0 g of solid L-proline was packed into the Omnifit column. The reactor was flushed with ethyl acetate prior to use. One stock solution was dispensed from pump A and the other stock solution was dispensed from pump B. Additional ethyl acetate was added using pump C and D or just C depending on total flow rate. The purpose of these experiments was to determine which reagents needed to flow through the packed bed of proline in order for the reaction to proceed efficiently. The following stock solutions were prepared.

Reaction 1 (Table 3.1, entry 1):

Reagents through column (pump A): 3 M hexanal solution in EtOAc

Reagents entering coil (pump B): 1 M nitrosobenzene

Volumetric ratios for pump A: pump B: ethyl acetate dilution → 1:1:29

Reaction 2 (Table 3.1, entry 2):

Reagents through column (pump A): 0.047 M **3b** solution in EtOAc

Reagents entering coil (pump B): 1 M nitrosobenzene, 3 M hexanal

Volumetric ratios for pump A: pump B: ethyl acetate dilution → 1:1:29

Reaction 3 (Table 3.1, entry 3):

Reagents through column (pump A): 3 M hexanal solution in EtOAc

Reagents entering coil (pump B): 1 M nitrosobenzene, 0.047 M **3b**

Volumetric ratios for pump A: pump B: ethyl acetate dilution → 1:1:29

Reaction 4 (Table 3.1, entry 4)

Reagents through column (pump A): 3 M hexanal and 0.047M **3b** solution in EtOAc

Reagents entering coil (pump B): 1 M nitrosobenzene, 0.1 M dodecane solution in EtOAc

Volumetric ratios for pump A: pump B: ethyl acetate dilution → 1:1:39

The following flow rates, depending on the volumetric ratios indicated above, were used for the pumps:

Residence time (minutes)	Pump A flow rate (mL/min)	Pump B flow rate (mL/min)	Pump C flow rate (mL/min) (1:1:29 ratio)	Pump C+D flow rate (mL/min) (1:1:39 ratio)
15	0.333	0.333	9.667	
15	0.333	0.333		13.0

For each reaction, the temperatures of both the column and the coil were set at 0ºC and a coil residence time of 15 minutes was used to assess each configuration. Once the system reached equilibrium, a fraction collector was used to collect diluted reaction mixtures (amount varied depending on dilution conditions) containing a theoretical product amount of 0.976 mmol. After collection the samples were poured into a suspension of sodium borohydride (148 mg, 3.9 mmol, 4 eq) in 10 mL of ethanol at 0ºC. The vials were rinsed with an additional 10 mL of ethanol and stirred for 30 min. 25 mL of saturated sodium bicarbonate was added and stirred, followed by 50 mL of water with further stirring. Any additional water was added to solubilize precipitation prior to extraction. The reaction mixture was then transferred to a separatory funnel, the layers

separated and the organic layer collected followed by extraction of the aqueous phase 2x with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The product was directly chromatographed with a gradient of 15% EtOAc/hexanes → 50% EtOAc/hexanes to afford the desired compound. The enantioselectivities were determined using chiral HPLC analysis.

5. General Screening Procedures (Table 3.2)

A stock solution of nitrosobenzene, and dodecane (used as an internal standard) was prepared in ethyl acetate. A separate stock solution of thiourea **3b** and hexanal in ethyl acetate was also prepared. A glass Omnifit column (6.6 mm diameter) is packed with 1.0 g of L-proline. The reactor setup was flushed with ethyl acetate prior to use. One stock solution was dispensed from pump A and the other stock solution was dispensed from pump B. Additional ethyl acetate was added using pumps C and D or just C depending on total flow rate. For each experiment the following solutions were prepared and reactor setup was programmed:

Reagents through column (pump A): 3 M hexanal and 0.047 M **3b** solution in EtOAc

Reagents entering coil (pump B): 1 M nitrosobenzene, 0.1 M dodecane solution in EtOAc (except Table 3.2, entry 2 did not contain dodecane)

Volumetric ratios for pump A: pump B: ethyl acetate dilution → 1:1:39

After the system reached equilibrium, a fraction collector was used to collect 40 mL of the diluted reaction mixture containing a theoretical product amount of 0.976 mmol. Immediately, after collection the samples were poured into a suspension of sodium borohydride (148 mg, 3.9 mmol, 4 eq) in 10 mL of ethanol at 0ºC. The vials were rinsed with an additional 10 mL of ethanol and stirred for 30 min. 25 mL of saturated sodium bicarbonate was added and stirred, followed by 50 mL of water with further stirring. Any additional water was added to solubilize precipitation prior to extraction. The reaction mixture was then transferred to a separatory funnel, the layers separated and the organic layer collected. The aqueous phase was extracted 2x with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The product was directly chromatographed with a gradient of 15% EtOAc/hexanes → 50% EtOAc/ hexanes to afford the desired compound. The enantioselectivities were determined using chiral HPLC analysis.

Residence time (minutes)	**Pump A flow rate (mL/min)**	**Pump B flow rate (mL/min)**	**Pump C or C+D flow rate (mL/min)**
10	0.500	0.500	19.5
15	0.333	0.333	13.0
20	0.250	0.250	9.75
25	0.200	0.200	7.80

6. Assessing Long Term Stability and Activity of the Proline Packed Bed (Figure 4)

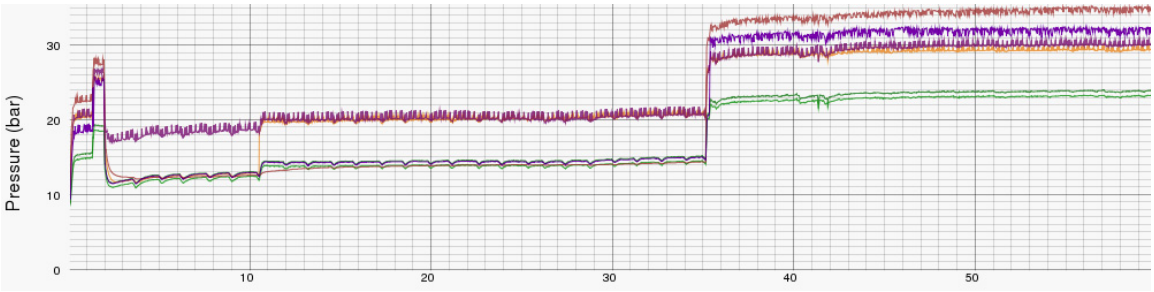
A glass Omnifit column (6.6 mm diameter) was packed with 1.00 g of L-proline and placed in the microreactor as described in the general setup. The column and tubing were flushed with ethyl acetate prior to use. A stock solution of nitrosobenzene (1 M) was prepared in ethyl acetate. A separate stock solution of thiourea **3b** (0.047 M) and

hexanal (3 M), in ethyl acetate were also prepared. One stock solution was pumped from pump A and the other stock solution was pumped from pump B. The reactor was programmed to run 80 mL of aldehyde/thiourea stock solution through the microreactor and periodically collect 20 mL fractions.

Immediately, after collection the desired samples were poured into a suspension of sodium borohydride (74 mg, 3.9 mmol, 4 eq) in 5 mL of ethanol at 0ºC. The vials were rinsed with an additional 5 mL of ethanol and stirred for 30 min. 12.5 mL of saturated sodium bicarbonate was added and stirred, followed by 25 mL of water and further stirring. Any additional water was added to solubilize precipitation prior to extraction. The reaction mixture was then transferred to a separatory funnel, the layers separated and the organic layer collected. The aqueous phase was extracted 2x with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The product was directly chromatographed with a gradient of 15% EtOAc/hexanes → 50% EtOAc/hexanes to afford the desired compound. Yields were plotted as a function of time where the time is plotted as the midpoint of the sampling interval. The enantioselectivities were determined using chiral HPLC analysis.

Residence time (minutes)	**Pump A flow rate (mL/min)**	**Pump B flow rate (mL/min)**	**Pump C flow rate (mL/min)**
20	0.250	0.250	9.750

7. Representative Pump Trace – Table 3.2, entry 9



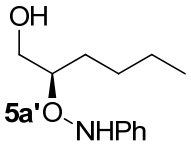
8. Product Characterization

General Reagent Configuration:

Reagents entering column (pump A): 3 M Aldehyde and 0.047 M **3b** in EtOAc

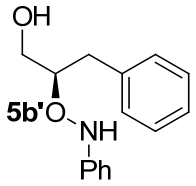
Reagents entering coil (pump B): 1 M nitrosobenzene in EtOAc

Reagents entering "quench" inlet: Ethyl Acetate

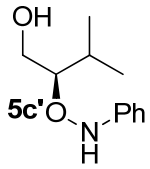


(*R*)-2-(*N*-phenylaminooxy)-hexan-1-ol (5a′). Prepared using the general reactor setup using hexanal (3.0 M) with a 0ºC packed bed L-proline column, 5ºC reactor coil, 20 minute coil residence time (pump A=0.250 mL/min, pump B=0.250 mL/min, pump C=9.750 mL/min), and a 1:1:39 (volumetric ratio for pump A: pump B: ethyl acetate dilution). 40 mL of product was collected (theoretical 0.976 mmol), reduced, and worked-up following the procedure described in section 5. The product was purified via flash column chromatography on silica gel using 15% EtOAc/hexanes followed by 50%

EtOAc/hexanes to afford the title compound as a yellow/orange oil (175.9 mg, 86% yield, 98% ee) ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.99 (m, 3H), 3.96 (m, 1H), 3.86 (dd, *J*=2.5, 12.0 Hz, 1H), 3.78 (dd, *J*=6.4, 12.1 Hz 1H), 2.58 (br s, 1H), 1.69 (m, 1H), 1.53 (m, 1H), 1.48-1.28 (m, 4H), 0.92 (t, *J*=7.1 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.7, 129.1, 122.4, 114.9, 84.1, 65.2, 29.8, 28.0, 23.0, 14.1 ppm.



(*R*)-3-phenyl-2-(*N*-phenylaminooxy)-propan-1-ol (5b′). Prepared according to the general reactor setup using hydrocinnamaldehyde (3.0 M) with a 0ºC packed bed L-proline column, 5ºC reactor coil, 10 minute coil residence time (pump A=0.500 mL/min, pump B=0.500 mL/min, pump C=9.750 mL/min) and a 1:1:19.5 (volumetric ratio for pump A: pump B: ethyl acetate dilution). 20.98 ml of diluted product was collected (theoretical 0.976 mmol), reduced, and worked-up following the procedure described in section 5. The product was purified via flash column chromatography on silica gel using 20% diethyl ether/pentane followed by 50% diethyl ether/pentane) to afford the title compound as a yellow oil (179.3 mg, 76% yield, 99% ee). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.34-7.15 (m, 7H), 7.04 (br s, 1H), 6.95 (m, 1H), 6.85 (m, 2H), 4.16 (m, 1H), 3.86 (dd, *J*=2.4, 12.0 Hz,1H), 3.74 (dd, *J*=5.9, 12.1 Hz, 1H), 3.06 (dd, *J*=6.8, 13.7 Hz, 1H), 2.86 (dd, *J*=7.1, 13.8 Hz, 1H), 2.38 (br s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.5, 138.1, 129.6, 129.1, 128.6, 126.6, 122.5, 114.8, 85.2, 64.2, 36.6 ppm.



(*R*)-3-methyl-2-(*N*-phenylaminooxy)-butan-1-ol (5c′). Prepared according to the general reactor setup using isovaleraldehyde (3.0 M) with a 40ºC packed bed L-proline column, 20ºC reactor coil, 20 minute coil residence time (pump A=0.200 mL/min, pump B=0.200 mL/min, and pump C=7.8 mL/min) and a 1:1:39 (volumetric ratio for pump A: pump B: ethyl acetate dilution). 40 mL of diluted product was collected (theoretical 0.976 mmol), reduced and worked-up following the general procedure described in section 5. The product was purified via flash column chromatography on silica gel using 15% EtOAc/hexanes followed by 50% EtOAc/hexanes to afford the title compound as a yellow/orange oil to afford the title compound as a yellow oil (146.6 mg, 77% yield, 97% ee). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.07 (br s, 1H), 7.03-6.96 (m, 3H), 3.87 (m, 2H), 3.74 (td, *J*=6.0, 3.0 Hz, 1H), 2.79 (br s, 1H), 2.03 (m, 1H), 1.05 (d, *J*=6.9 Hz, 3H), 1.00 (d, *J*=6.9 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.5, 129.2, 122.8, 115.3, 88.9, 64.0, 29.0, 19.0, 18.8 ppm.

See Appendix 2 for copies of GC/HPLC chromatograms and corresponding chiral methods as well as ^{1}H and ^{13}C NMR spectra.

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CHAPTER 4

Use of Solids in Flow: Continuous Synthesis and use of N-Heterocyclic Carbene-Copper(I) Complexes

Preface

As an extension of the flow work presented in the previous chapter, this chapter aims to implement the use of a packed-bed reactor in the synthesis of N-heterocyclic carbene copper (I) complexes. Again, the success of this work relies on the use of a solid insoluble starting material (copper oxide) that upon reaction with an imidazolium or imidazolidinium precursor become soluble and can be used for downstream reactions for air sensitive/unstable compounds, catalyst screening or implemented for large scale synthesis for bench stable compounds.

Introduction*

Transition metal catalysts are an important tool in the efficient, atom economical and selective synthesis of molecules.[1, 2] Recent increases in the cost of precious metals and a focus on greener more sustainable syntheses has spurred research into developing highly reactive catalysts with Earth abundant, less toxic metals, such as copper, iron, molybdenum, and tungsten.[3] Obtaining the high turn-over-numbers (TON) often observed with precious metals has placed a greater emphasis on identifying ligands that control the reactivity and selectivity of the desired transformations. N-heterocyclic carbene (NHC) ligands[4-11] have emerged as an alternative, highly active set of ligands resulting in more air- and moisture-stable complexes.

* The author thanks Dr. Jin Kyoon Park and Ashley Longstreet for their contributions to this soon to be published work.

Despite the relative improved stability of NHC-metal complexes, their synthesis and use often requires Schlenk techniques or a glove box.[12, 13] Though these techniques have lead to outstanding discoveries and continued innovation, they are difficult/expensive to scale, time-intensive, and require specialized training and safety measures.[14] In order to overcome these drawbacks, we speculated that flow chemistry[15-17] could provide a new strategy for efficiently handing and screening air sensitive[18] transition metal complexes (Figure 4.1).

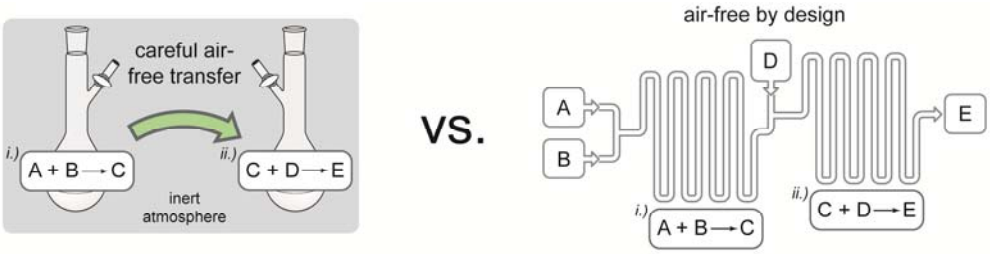


Figure 4.1: Traditional air free techniques require manipulation using Schlenk techniques or a glove box. Continuous chemistry provides an environment with limited air contact.

Continuous-flow chemistry has advantages relative to batch methods including rapid mixing and heat transfer. Though these methods are omnipresent in oil-refining and bulk-chemical manufacturing, application of flow chemistry in the synthesis of fine, pharmaceutical and now natural product synthesis is becoming commonplace.[19-22] With their noted high activity and widespread use, developing a single streamlined method for rapidly synthesizing and using Copper(I)-NHC complexes without cumbersome air-free techniques would aid in the development of new chemical transformations.

Copper(I)-NHC complexes are often prepared by generating the carbene *in situ* from an imidazolium or imidazolidinium salt using a strong base followed by addition of a copper (I) source under inert conditions.[12, 13] Recognizing the need for a protocol that avoided strong base or expensive soluble copper source, Citadelle[23] and Chun[24] simultaneously reported that imidazolium or imidazolidinium salts refluxed in copper (I) oxide overnight produced NHC-Cu(I)-halide complexes. Though an excellent step forward, the implementation of copper (I) oxide or other readily available, inexpensive metal source in flow would prove challenging as the majority of continuous chemistry, is limited to homogeneous reactions or those with supported reagents and catalysts. While a few examples exist[15, 25-31], the use or generation of solids in flow is often avoided due to high probability of pump or reactor clogging.

Our group has had a long-standing interest in the manipulation and production of solids in flow,[32-36] including our recent work demonstrating that a proline packed-bed could react with an aldehyde to generate a soluble catalyst for subsequent α-aminoxylation.[37] We are also active in Earth abundant metal catalysis and recently designed a novel NHC-Cu(I) catalyst.[38-40] Combining these prior experiences, we postulated that NHC-Cu(I) halide complexes could be prepared by passing a soluble imidazolium or imidazolidinium salt through a packed-bed of copper (I) oxide yielding a soluble active catalyst (Figure 4.2). Additionally, we speculated that the packed-bed would increase the rate of complex formation due to improved surface contact. Herein, we demonstrate that this packed-bed approach is a valuable method as both known, new, air sensitive, and chiral Cu(I) complexes are produced with residence times of <5 mins in high yield and purity. Furthermore, we illustrate the utility of this setup by generating a copper (I) complex and using it in subsequent downstream β-borylation reaction.

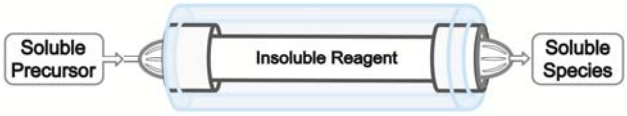
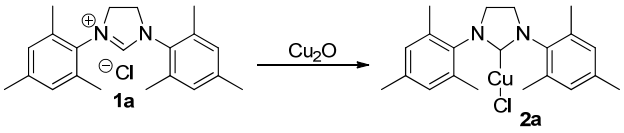


Figure 4.2: An Overview of the pre-catalyst approach

Results and Discussion

We employed a Vapourtec R series reactor system[41] equipped with HPLC pumps for solvent and reagent inputs, a heated tube reactor containing a glass Omnifit column, and fraction collector to test our hypothesis. We found that simply packing an Omnifit column with commercially available copper (I) oxide (<5μm particle size) and passing a solution of imidazolidinium salt **1a** through was unsuccessful because copper (I) oxide particulates leached out of the column due to the fine particle size (Scheme 4.1). Though we could purchase copper (I) oxide with better defined particle size, our goal was to use readily available, inexpensive copper (I) oxide. To this end, we predicted that diluting the copper (I) oxide in a solid diluent and packing the pure diluents at the each end of the packed-bed would prevent fines from leaching (Figure 4.3).



Scheme 4.1: Reaction of imidazolidinium salt **1a** with copper (I) oxide.

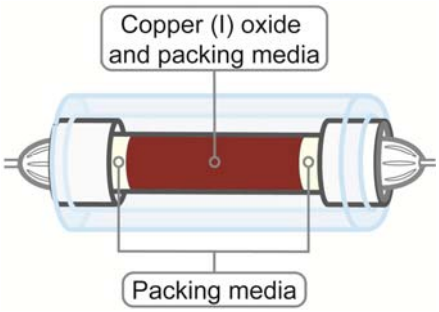


Figure 4.3: Packing of the column

As expected, addition of diluents such as silica gel, reverse phase silica gel and molecular sieves all produced a packed-bed that prevented fine copper (I) oxide from passing through. We found that 4Å molecular sieves provided the best diluent from a cost and performance standpoint as this material not only filtered fines, but also simultaneously removed water produced during the reaction.[42] We were pleased that at 110ºC and a flow rate of 0.800 ml/min, corresponding to ~2 min residence time, provided >95% yield in an 80% CH_2Cl_2/20% toluene mixture (Table 4.1, entry 1).

To better understand the system, we measured the conversion of starting material to product as a function of column temperature. We found a very steep temperature dependence. At temperatures below 60^{o}C, the reaction does not proceed at a detectable level. The reaction onset begins above 60^{o}C and shows maximum product formation at 110^{o}C (Figure 4.4).

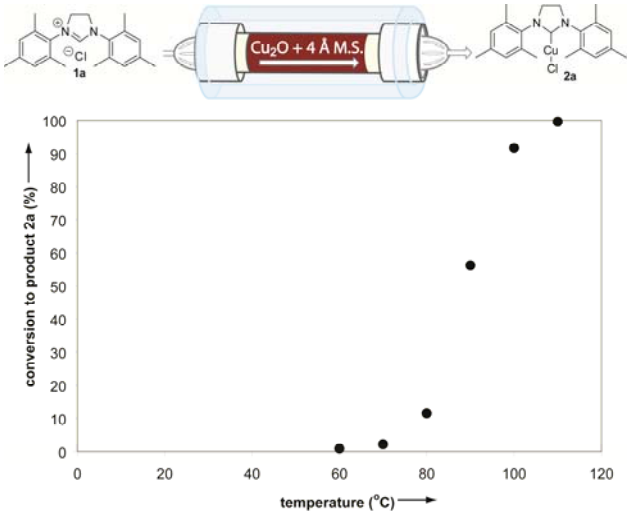
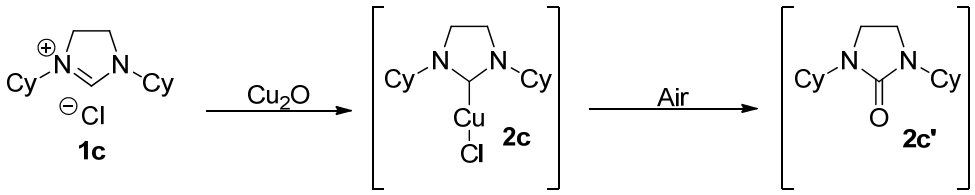


Figure 4.4: Effect of temperature on the reaction conversion using a flow rate of 0.800 mL/min (~2 minute residence time), 80% CH_2Cl_2/20% toluene. Each data point is an average of three runs on the same copper (I) oxide column.

With an understanding of the parameters affecting complex formation, other imidazolium/imidazolidinium salts were investigated. A 2 minute residence time and a 110ºC column temperature were suitable for most substrates. We found this method performed well for the commonly used imidazolium salt **1b**, providing >95% yield with a 2 minute residence time (Table 4.1 entry 2). We then sought to prepare more challenging substrates. Previous studies found that subjecting imidazolidinium salt **1c** to copper (I) oxide in refluxing toluene resulted in only a cyclic urea product (**2c'**). With this in mind, we subjected **1c** to our reactor setup. We found that collecting the product under an inert atmosphere was critical to prevent degradation and were delighted to find 86% yield with a 4 minute residence time after filtration through silica gel yielded a white solid (Table 4.1, entry 3). We observed a 20% increase in cyclic urea product **2c'** upon stirring product **2c** under a balloon of air overnight. We

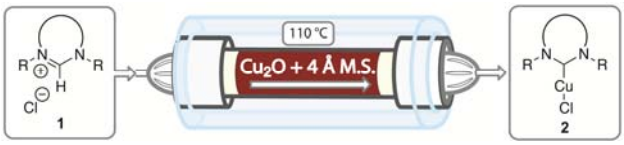
speculate that Citadelle's conditions most likely provide the desired complex **2c**, but decompose readily (Scheme 4.2).

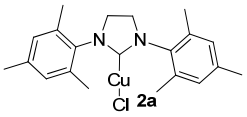
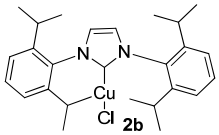
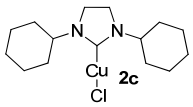
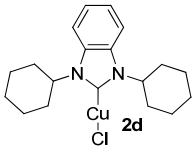
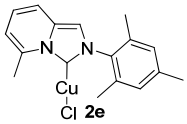
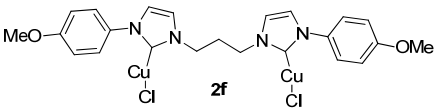


Scheme 4.2: Potential decomposition pathway of complex **2c**.

We were also able to successfully prepare a fused cyclic copper (I) complex **2d** (Table 4.1, entry 4) as well as a copper catalysts with imidazo-[1,5-a]pyridine type skeletons (Table 4.1, entry 5). Finally we established this method was a viable strategy for the synthesis of homobimetallic copper (I) complexes as well (Table 4.1, entry 6).

Table 4.1: NHC-Cu(I)-chloride complexes prepared using general packed-bed approach from imidazolium-type chloride salts.



Entry	Product	Yield (%)[a]
1[b]	 **2a**	>95
2[c]	 **2b**	>95
3[b]	 **2c**	86[d]
4[b]	 **2d**	91
5[b]	 **2e**	91
6[c]	 **2f**	88

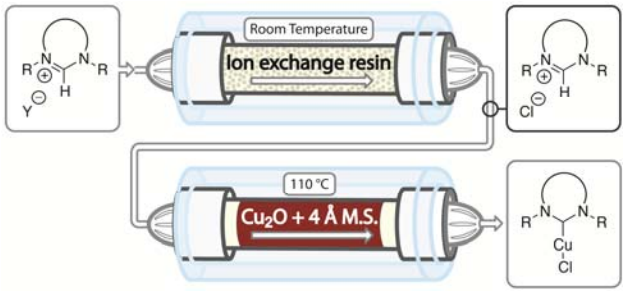
[a]Isolated yield. [b]A 80% CH_2Cl_2/20% toluene mixiture was used as a solvent. [c]Due to solubility of salts, 5% MeOH/80% CH_2Cl_2/15% toluene was used. [d]Collected under argon. See supporting information for detailed reaction conditions.

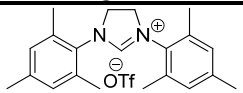
Like others, when we passed triflate **3** and tetrafluoroborate **4** imidazolidinium salts through our copper (I) oxide/4Å molecular sieves column we found no appreciable reaction occurred. Since copper (I) oxide is used for labile imidazolidinium salts, complexes from weakly coordinating anions such as OTf⁻ and

BF_4^- would prove challenging with alternative carbene forming methods. While many substrates can be prepared with a different counterion, there are some whose synthetic strategy limits their availability.

We hypothesized that a setup with a tandem ion exchange/complex formation could readily transform weakly coordinating copper salts. We packed an Omnifit column with an ion exchange resin and placed it in-line with a copper (I) oxide column. After washing the resin with a series of solvents to remove water, we found less than 60% conversion to product using an 80% CH_2Cl_2/20% toluene solution. However, the addition of 5% MeOH to the stock solution resulted in full conversion to the desired product. Flowing triflate **3** or BF_4^- **4** salt through the columns at a rate of 0.800 mL/min resulted in 95% yield to the desired **2a** complex (Table 4.2, entries 1,2). Thus, with our combined ion exchange and complex generation protocol other labile salts with weakly coordinating ions could be realized using milder copper (I) oxide conditions.

Table 4.2: NHC-Cu(I)-chloride complexes prepared using tandem ion exchange/Cu_2O packed-bed



Entry	Starting Material	Yield (%)[a]
1	 **3**	95
2	 **4**	95

[a]Isolated yield.

We envisioned our protocol could be used as both a method for rapidly producing gram quantities of catalysts as well as placed in-line for subsequent reaction. Designing a catalyst screening protocol that rapidly generates complexes and allows for immediate testing is highly desirable. Flow chemistry methods that employ supported catalysts are not convenient for catalyst screening in new reactions as the synthesis of tethered active analogs can be time-consuming and only solvents that provide appropriate swelling properties can be used.[43-47] Our packed-bed approach allows for rapid screening of catalysts for a process before a supported analog is designed. As proof of utility we examined the activity of a copper (I) oxide column with a 0.02M solution of imidazolidinium salt **1a**, as this is a typical concentration one might use for performing downstream reactions. We continually passed solution through the column and observed sustained output of complex **2a** (Figure 4.5A). Next we wanted to maximize the output of the reactor by increasing the concentration

of the imidazolidinium salt **1a** by 10 fold to 0.2M. The reactor was run continuously for ~1 hour. Samples were periodically collected, concentrated, and assessed for conversion. We found ~1.0 g of complex **2a** was produced in 16 minutes before we observed a decrease in yield (Figure 4.5B). These outcomes indicates that our protocol would be a useful strategy for both generating and screening carbene catalysts in downstream flow process as well as isolating and storing the complexes for future use.

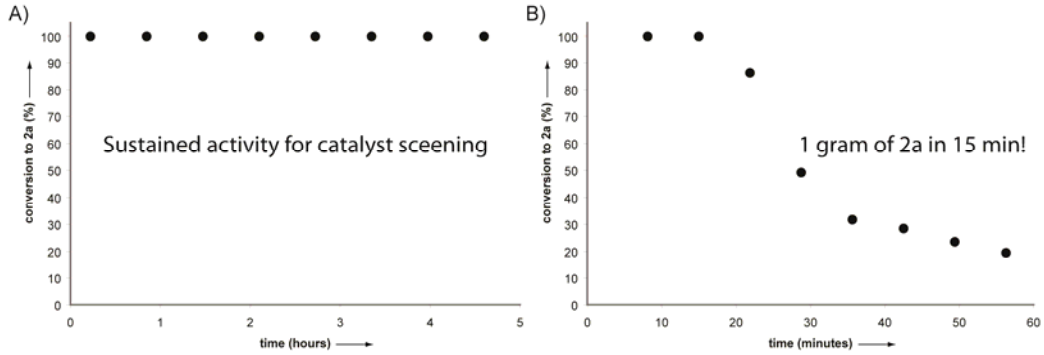


Figure 4.5: The long-term stability of a copper (I) oxide/4Å molecular sieve packed-bed for the formation of complex **2a**. **A)** A 0.02M **B)** 0.2M solution of imidazolidinium salt **1a** (80% CH_2Cl_2/ 20% toluene) was passed through a packed-bed of copper (I) oxide/4Å molecular sieve (1:1 by weight) (entering at the bottom of the column and exiting at the top) at 110ºC with a flow rate of 0.800 ml/min corresponding to a ~2 minute residence time. Samples were periodically collected, concentrated and assessed for conversion to product by ^{1}H NMR.

To illustrate our method's utility, we explored the catalytic activity of the copper complexes by employing them in β-borylation reactions. Due to the ease of synthesis of the salt **1a** it was first examined in the β-borylation of ethyl crotonate.

The same setup to generate the catalyst was employed; however, a 2 mL cooled coil (0ºC) and additional pumps were added to the setup to introduce the starting materials (Figure 6). Using a 0.800 mL/min flow rate of ligand **1a** (~2 minute residence time in copper oxide column) we were able to produced 79% yield of borylated product **7a**.

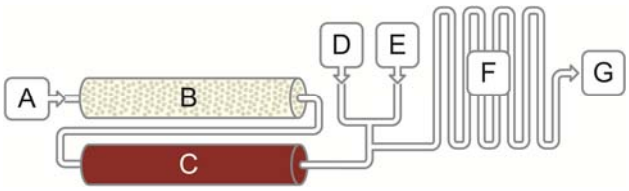
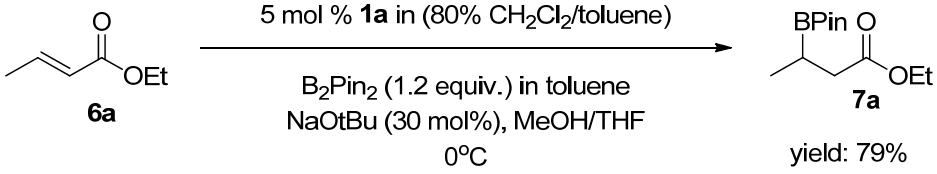


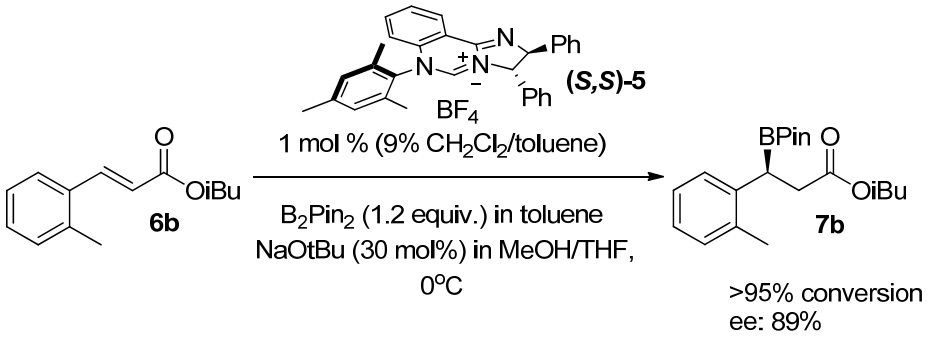
Figure 4.6: Composite reactor setup for performing NHC-copper catalyzed β-borylation reaction in flow. Imidazolidinium salt enters at A, flows through an optional ion exchange resin (B), followed by Cu_2O/4Å molecular sieve column. The complex is then pre-cooled in coil F, and combined with a pre-cooled solution of B_2Pin_2, ester and NaOtBu (D+E). The product is then collected (G).



Scheme 4.3: β-borylation of ethyl crotonate using the above reactor setup *without* the ion exchange column.

As a final illustration of the power of this setup we performed the β-borylation of an ortho-substituted cinnamate ester with chiral 6-NHC-ligand **5**. Due to the synthetic strategy used in its synthesis, the BF_4^- salt was only available. Thus, we envisioned a setup with an in-line ion-exchange to prepare the chloride salt in-situ. Due to the high

turn over numbers observed with this catalyst we wanted to use only 1 mol% of the salt. Reactions were performed by passing a solution of 6-NHC ligand **5** through an ion exchange resin followed by reaction in a copper oxide column at 110ºC. Preliminary results indicate that subsequent β-borylation in a 0ºC coil, provided >95% conversion to the desired product **7b** by GC with 89% ee after oxidation (Scheme 4.4, Figure 4.7).[48]



Scheme 4.4: Enatioselective β-borylation of ortho-substituted cinnamate ester with a chiral 6-NHC-ligand **5** using the above reactor setup *with* the ion exchange column.

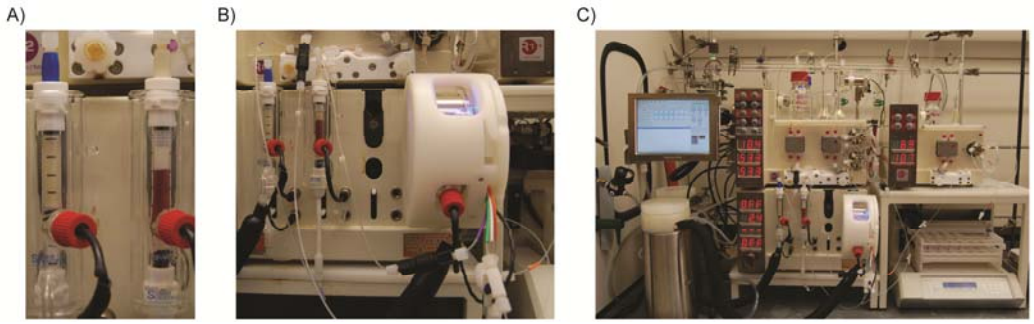


Figure 4.7: Composite reactor setup for performing copper carbene catalyzed β-borylation reactions. **A)** Glass Omnifit columns are packed with ion exchange resin (optional) and copper (I) oxide and molecular sieves (1:1 by weight). **B)** The columns are placed in-line with a cooled 2 mL PFA coil tube reactor. **C)** The components are connected to HPLC pumps for solvent and reagent inputs. A computer is programmed to control the timing of reagent/solvent inputs and fraction collection.

Conclusion

In conclusion, we have demonstrated a facile method to convert insoluble inorganic catalyst precursors into copper carbene catalysts using solid copper (I) oxide and solutions of imidazolium-type precursors. The success of this chemistry relies on the use of a packed-bed of a solid catalyst precursor that becomes soluble upon complex formation. The use of traditionally available flow chemistry methods with copper (I) oxide would have been impossible for this type of reaction due to subsequent reactor clogging. We also provide an option for synthesizing copper-chloride complexes from other imidazolium-type salts by employing an ion exchange resin. This innovation is particularly useful for the synthesis of NHC-copper-chloride complexes readily available from non-halide containing salts. We illustrated the usefulness of this approach by performing both a racemic and chiral β-borylation reaction. We envision this setup will be useful in the rapid generation and screening of NHC-copper catalysts in the discovery of new reactions and are currently exploring the possibility of linking complex formation with catalyst testing/use in other reactions.

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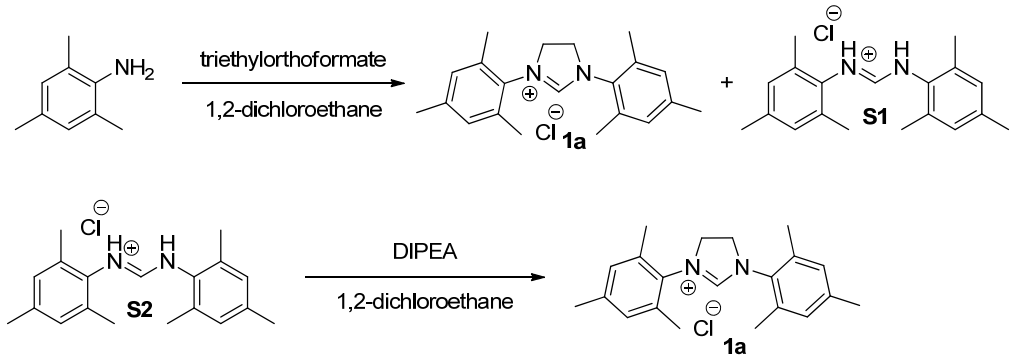
1. General Information

Flash chromatography was performed using silica gel (230-400 mesh). For analytical thin layer chromatography (TLC), silca gel 60 F_{254} plates were used. All commercial reagents were used without further purification with the following exceptions. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on 600 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p=pentet, hept=heptet, m = multiplet), coupling constants in Hertz (Hz), integration.

Reactions were performed with a commercially available Vapourtec R series reactor controlled by FlowCommander™ software. Mixtures of solid copper oxide and filler material were packed into a glass Omnifit column (6.6 mm diameter) fitted with Vapourtec end caps and PTFE frits. All tubing and fittings were supplied with the reactor, but the tubing was standard 1.00 mm bore PFA and standard PTFE fittings.

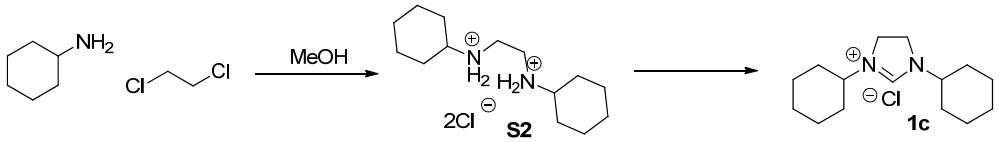
The following starting materials were purchased: 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride (**1b)**, 1,3-Dicyclohexylbenzimidazolium chloride (**1d)**, 2-Mesityl-5-methylimidazo[1,5-a]pyridinium chloride (**1e)**, 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (**4)**, We previously reported the synthesis of 6-membered ring NHC Imidazoquinazolium salt (**5)**[39] and (E)-isobutyl 3-(o-tolyl)acrylate **(6b)**.[39]

2. Reactant Synthesis



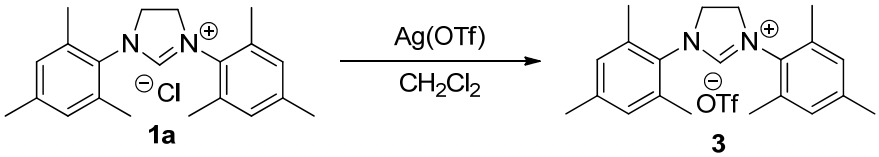
1,3-dicyclohexyl-4,5-dihydro-1H-imidazol-3-ium chloride (1a). Triethyl orthoformate (6.2 mL, 37 mmol, 1 equiv), 2,4,6-trimethylaniline (10.4 mL, 74 mmol, 2 equiv), and 1,2-dichloroethane (20.4 mL, 259 mmol, 7 equiv) were charged to a Schlenk flask. The flask was evacuated until the solvent began to boil, sealed under static vacuum, then heated to 120 °C. After 25 h, the reaction mixture was cooled and excess reagents were removed *in vacuo*. The viscous liquid was dissolved in a minimal amount of dichloromethane, then the product was triturated out of boiling toluene and collected by vacuum filtration to yield **1c** (3.95 g, 31%) as a white solid. A mixture of remaining **1a** and **S1** recrystallized from the toluene filtrate once cooled and was collect by vacuum filtration (4.60 g). To a solution of the **1a** and **S1** mixture in 1,2-dichloroethane (11.4 mL, 145 mmol, 10 equiv) in a Schlenk flask was added N,N-diisopropylethylamine (5.6 mL, 31.9 mmol, 2.2 equiv). The flask was evacuated until the solvent boiled, sealed under static vacuum, then heated to 120 °C. After 48 h the flask was cooled and excess reagents were removed *in vacuo*. The viscous liquid was dissolved in a minimal amount of dichloromethane and the product was triturated out of boiling toluene. **1a** (3.75 g, 30%) was collected by vacuum filtration as a white solid. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.67 (s, 1H), 6.87 (s, 4H), 4.48 (s, 4H), 2.32 (s, 12H), 2.25 (s, 6H) ppm. ^{13}C NMR: (151 MHz, $CDCl_3$) δ 160.1, 139.9, 134.8, 130.2,

129.6, 51.7, 20.8, 17.8 ppm.



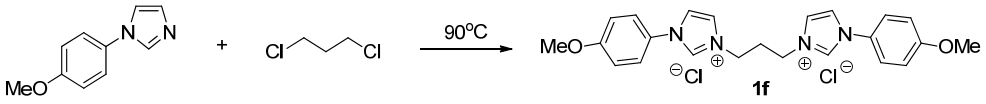
1,3-dicyclohexyl-4,5-dihydro-1H-imidazol-3-ium chloride (1c). To a solution of cyclohexylamine (8.5 mL, 74 mmol, 2.2 eq) in methanol (6.7 mL) was added 1,2-dichloroethane (2.7 mL, 33.6 mmol, 1 eq). The solution was heated to reflux for 48 h. The cooled reaction mixture was poured into 150 mL of vigorously stirring acetone. The white solid was collected by vacuum filtration and recrystallized in ethanol/H_2O to give **S1** (3.47 g, 35%) as a white solid. ^{1}H NMR: (600 MHz, D_2O) δ 3.40 (s, 4H), 3.16 (m, 2H), 2.06 (br d, *J*=10.6 Hz, 4H), 1.81 (br d, *J*=12.9 Hz, 4H), 1.63 (m, 2H), 1.31 (m, 8H), 1.15 (m, 2H) ppm. ^{13}C NMR (151 MHz, D_2O) δ 58.1, 40.2, 28.8, 24.4, 23.9 ppm.

To a 10 mL pressurized microwave vessel equipped with a stir bar was added **S2** (1.0 g, 3.4 mmol, 1 eq) and triethylorthoformate (2.5 mL, 15 mmol, 4.46 eq). The vessel was capped and irradiated for 6 min at a temperature set to 145 °C at 75 W microwave power (no ramp was applied). The reaction mixture was diluted in diethyl ether (20 mL), and **1c** (0.72 g, 79%) was collected as a white solid by vacuum filtration. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.72 (s, 1H), 3.99 (s, 4H), 3.82 (tt, *J*=5.83 Hz , 2H), 2.02 (br d, *J*=11.29 Hz, 4H), 1.84 (br d, *J*=13.93 Hz, 4H), 1.66 (br d, *J*=13.55 Hz, 2H), 1.49 (dq, *J*=4.08 Hz, 4H), 1.35 (tq, *J*=4.33 Hz, 4H), 1.15 (tq, *J*=13.05 Hz, 2H) ppm. ^{13}C NMR: (151 MHz, $CDCl_3$) δ 154.2, 57.3, 45.3, 31.0, 24.7 ppm.



1a 3

1,3-Bis(2,4,6-trimethylphenyl)imidazolinium triflate (3). Silver trifluoro methanesulfonate (2.25 g, 8.75 mmol, 2.0 eq) was dissolved in CH_2Cl_2 (18 mL) and MeOH (10mL). Then 1,3-Bis(2,4,6-trimethylphenyl)imidazolinium chloride **1a** (1.5 g, 4.37 mmol, 1.0 eq) was added. The reaction was stirred at room temperature for 1.25 hours. The resulting suspension was filtered thorough celite, and rinsed with CH_2Cl_2. The resulting solution was concentrated, re-dissolved in dichloromethane, filtered through a 0.2μm PTFE membrane and washed with water 3x. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield the desired triflate salt **3** (1.0236 g, 51% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.27 (s, 1H), 6.94 (s, 4H), 4.46 (s, 4H), 2.32 (s, 12H), 2.29 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.4, 140.7, 134.9, 130.04, 130.01, 120.6 (q, J=320.6), 51.7, 21.0, 17.57. The ^{1}H NMR and ^{13}C NMR data were in accordance with those described in the literature.[49]



1f

3,3'-(propane-1,3-diyl)bis(1-(4-methoxyphenyl)-1H-imidazol-3-ium) chloride (1f): 1-(4-methoxyphenyl)-1H-imidazole (598.4 mg, 3.44 mmol, 2.5 eq) and 1,3-dichloropropane (130 μl, 1.374 mmol, 1.0 eq) were added to a vial equipped with a stir bar. Upon heating to 90°C overnight a hard substance formed. The reaction was cooled to room temperature and the product was precipitated from

MeOH/CH_2Cl_2/methyl *tert*-butyl ether to yield an off-white powder (538.6 mg, 96% pure with residual solvent as impurity, 82% yield). ^{1}H NMR: (600 MHz, CD_3OH) δ 9.68 (br m, 2H), 8.08 (t, J=1.74 Hz, 2H), 7.99 (t, J=1.71 Hz, 2H), 7.72 (m, 4H), 7.18 (m, 4H), 4.59 (t, J=7.32 Hz, 4H), 3.91 (s, 6H), 2.77 (p, J=7.34 Hz, 2H) ppm. ^{13}C NMR (151 MHz, CD_3OH) δ 162.5, 136.7, 129.4, 125.0, 124.5, 123.5, 116.5, 56.4, 48.2, 31.3 ppm.

3. Reactor Setup

A) Preparation of copper oxide column

A vial containing 2.0 g of activated 4Å molecular sieves and 2.0 g of copper (I) oxide powder (<5μm particle size) was mixed using a vortex mixer for 2x30s. The resulting powder was gently mixed with a spatula prior to use to ensure a uniform sample. To a glass Omnift column (6.6 mm diameter) 440 mg of activated 4Å molecular sieves was added to the column and packed tightly with a glass rod. Then 1.65 g of the copper (I) oxide/4Å molecular sieve mixture was gently packed into the column. An additional 275 mg of 4Å molecular sieves was packed on top of the column and the cap secured. To determine the void volume of the column toluene was flushed through the system at 1.00 ml/min for ~30 min. The void volume was measured to be 1.6mL and was assumed for all experiments. The column was then flushed with 80% CH_2Cl_2/toluene for ~30 minutes at 1.00 mL/min. Upon packing a void appeared at the top of the column, but the cap was left in place.

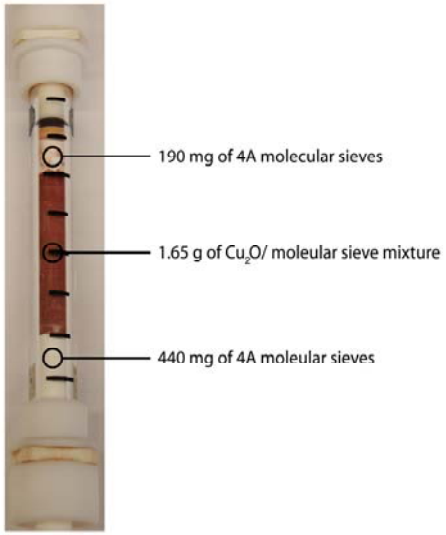
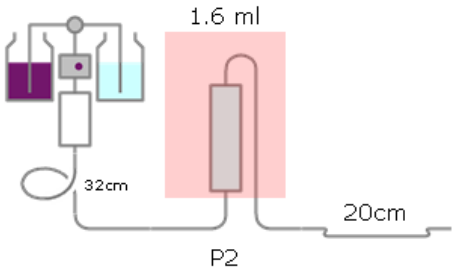


Figure 4.8: Column after packing the molecular sieves and copper oxide into an omni fit column.

B) Reactor Configuration



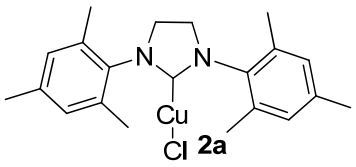
Description from left to right: One pump was connected with 32 cm of drop tubing to the **bottom**[50] of a glass Omnifit column (6.6 mm diameter) containing 1.65 g of the copper (I) oxide/4Å molecular sieve plus the molecular sieve endcaps (as outlined above) with a void volume ~1.6 mL. An additional 20 cm of tubing connected the **top** outlet of the column to a 100 psi backpressure regulator (not shown) and extra tubing to reach a fraction collector.

4. Experiments to assess the influence of column temperature

The column and reactor were assembled as described above. The setup was first flushed with toluene to determine the void volume of the column and then an 80% CH_2Cl_2/ 20% toluene solution. A stock solution of **1a** (0.020M) was prepared in an 80% CH_2Cl_2/ 20% toluene solution. A series of experiments were performed to assess the conversion of the reaction to product at a given column temperature using a flow rate of 800 uL/min corresponding to ~2 minute residence time. After the system reached equilibrium 6.5 mL of product stream was collected with a theoretical maximum of 130 μmol of product. The vials were concentrated, dried under nitrogen for 15 minutes, and dried under vacuum. Conversion to product was assessed by ^1H NMR by integrating the product and starting material peaks in relationship to each other.

5. Substrate Scope and Product Characterization

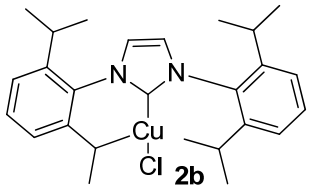
The general reactor setup was used as described above. The same copper oxide/molecular sieve column was reused for multiple substrates with only washing of solvent in between uses. Stock solutions containing 0.020M substrates were passed through the column and 10 mL of product was collected with a theoretical maximum of 0.200 mmoles expected.



2a

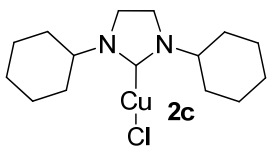
(1,3-dimesitylimidazolidin-2-yl)copper(I) chloride 2a: Prepared according to

general reactor setup. The solution was concentrated and dried to yield **2a** (80.0 mg, 98% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (s, 4H), 3.95 (s, 4H), 2.31 (s, 12H), 2.29 (s, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.6, 138.6, 135.5, 135.0, 129.8, 51.0, 21.1, 18.1 ppm. The ^{1}H NMR and ^{13}C NMR data were in accordance with those described in the literature.[12]



2b

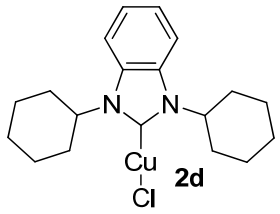
(1,3-bis(2,6-diisopropylphenyl)-2,3-dihydro-1H-imidazol-2-yl)copper(I) chloride 2b: Prepared according to general reactor setup except a 5% MeOH, 80% CH_2Cl_2, 15% toluene stock solution was used due to solubility of starting material. The solution was concentrated and dried to yield **2b** (96.6 mg, >95% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (t, J = 7.8 Hz, 2H), 7.29 (d, J = 7.8 Hz, 4H), 7.13 (s, 2H), 2.56 (hept, J = 6.9 Hz, 2H), 1.30 (d, J = 6.9 Hz, 12H), 1.23 (d, J = 7.0 Hz, 12H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.6, 145.6, 134.4, 130.6, 124.2, 123.2, 28.7, 24.8, 23.9 ppm. The ^{1}H NMR and ^{13}C NMR data were in accordance with those described in the literature.[51]



2c

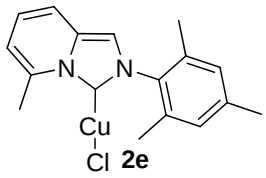
(1,3-dicyclohexylimidazolidin-2-yl)copper(I) chloride 2c: General reactor setup used, however, the flow rate was decreased to 0.400 mL/min (~4 min residence time).

Additionally, the fraction collector was disconnected and the product was collected under argon and further dried under nitrogen. It was filtered through silica gel with CH_2Cl_2 under nitrogen to obtain a white solid that upon sitting in a capped vial degrades to a green gel. (58 mg, 86% yield, 99% purity with CH_2Cl_2 as main contaminant, purity decreases over time to give ^{1}H NMR peaks assumed to be cyclic urea). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.89-3.80 (m, 2H), 3.51 (s, 4H), 1.86-1.75 (bs, 8H), 1.67 (m, 2H), 1.49 (m, 4H), 1.37 (m, 4H), 1.09 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.5, 59.7, 44.2, 32.0, 25.3, 25.2 ppm.



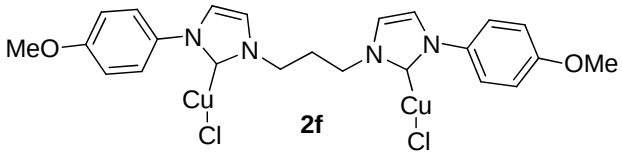
2d

(1,3-dicyclohexyl-2,3-dihydro-1H-benzo[d]imidazol-2-yl)copper(I) chloride 2d: Prepared according to general reactor setup. The solution was concentrated and dried to yield **2d** (69.3 mg, 91% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 2H), 7.36 – 7.33 (m, 2H), 4.49 (tt, *J* = 12.3, 3.8 Hz, 2H), 2.42 (qd, *J* = 12.5, 3.3 Hz, 4H), 2.09 (d, *J* = 11.5 Hz, 4H), 2.00 (d, *J* = 13.5 Hz, 4H), 1.80 (d, *J* = 12.9 Hz, 2H), 1.54-1.46 (m, 4H), 1.39 (qt, *J* = 12.9, 3.4 Hz, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.2, 133.2, 123.5, 111.8, 59.7, 33.9, 26.1, 25.2 ppm.



2e

(2-mesityl-5-methyl-2,3-dihydroimidazo[1,5-a]pyridin-3-yl)copper(I) chloride 2e: Prepared according to general reactor setup. The solution was concentrated and dried to yield **2e** (64.1 mg, 91% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 9.2 Hz, 1H), 7.29 (s, 1H), 7.00 (s, 2H), 6.94 (dd, J = 9.2, 6.6 Hz, 1H), 6.58 (d, J = 6.5 Hz, 1H), 3.11 (s, 3H), 2.36 (s, 3H), 1.99 (s, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 139.6, 136.7, 136.2, 134.3, 131.9, 129.4, 123.3, 115.9, 114.0, 112.7, 22.4, 21.1, 17.7 ppm.



2f

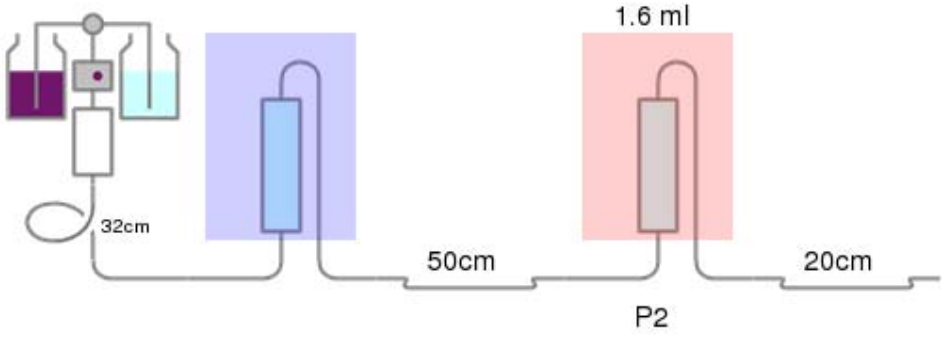
1,3-bis(3-(4-methoxyphenyl)-2,3-dihydro-1H-imidazol-1-yl)propyl copper (I) chloride (2f). Prepared according to general reactor setup except a 5% MeOH, 80% CH_2Cl_2, 15% toluene stock solution was used due to solubility of starting material. (105.6 mg, 98% purity with CH_2Cl_2 as contaminant, 88% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 4H), 7.26 – 7.21 (m, 4H), 7.02 – 6.96 (m, 4H), 4.34 (t, J = 7.0 Hz, 4H), 3.85 (s, 6H), 2.69 (p, J = 7.0 Hz, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 132.6, 125.0, 123.7, 122.1, 121.2, 115.0, 55.7, 48.6, 32.6 ppm (missing Cu-C peak due to low solubility and sensitivity).

6. General Reactor Setup Using Ion Exchange Resin

A) Preparation of ion exchange column:

A glass Omnifit column (6.6 mm diameter) was packed to a height of ~6 cm with Dowex 1x4, 200-400 mesh ion exchange resin by first suspending the resin in MeOH and packing by vacuum filtration and lightly packing with a glass rod. The end-cap was secured and the water was removed by running MeOH and acetone sequentially through the column for ~20 minutes at 1.00 mL/min. Then 80% CH_2Cl_2/5% MeOH/15% toluene was run through the column for ~20 minutes at 1.00 mL/min, the top was cinched down, and additional solvent was run through the column.

B) Reactor Configuration

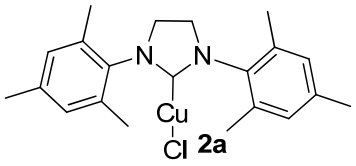


Description of from left to right: One pump was connected with 32 cm of drop tubing to the **bottom** of a glass Omnit fit column (6.6 mm diameter) containing ion exchange resin packed as described above with an assumed void volume of 1.6 mL. An additional 50 cm of tubing connected the top outlet of the ion exchange column to the **bottom** of a glass Omnifit column (6.6 mm diameter) containing 1.65 g of the

copper (I) oxide/4Å molecular sieve (as outlined above) with a void volume ~1.6 mL. An additional 20 cm of tubing connected the **top** outlet of the column to a 100 psi backpressure regulator (not shown) and extra tubing to reach a fraction collector.

7. Substrate Scope and Product Characterization with Ion Exchange Resin

The general reactor setup as described in section 6b was used. The same ion exchange column and copper oxide/molecular sieve column was reused for multiple substrates with only washing of solvent in between uses. Stock solutions containing 0.020M of substrate was passed through the column and 10 mL of product was collected with a theoretical maximum of 0.200 mmoles expected.



2a

From triflate salt **3** (77.2 mg, 95% yield). The ^{1}H NMR data matched those obtained above for substrate **2a**. (see above)

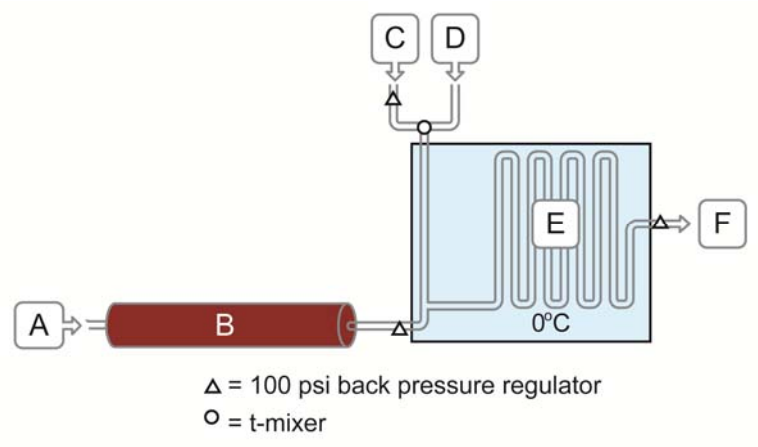
From tetrafluoroborate salt **4** (77.6 mg, 95% yield). The ^{1}H NMR data matched those obtained above for substrate **2a**. (see above)

8. Long Term Stability Experiments

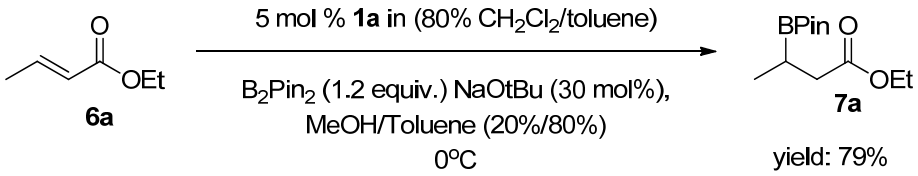
A glass Omnifit column (6.6 mm diameter) containing 1.65 g of the copper (I) oxide/4Å molecular sieve (prepared as described outlined above) with a void volume ~1.6 mL was setup in the microreactor according to section 3A/3B. A stock solution of **1a** (0.2M) or (0.02M) was prepared in 80% CH_2Cl_2/toluene. The reactor was programmed to continuously run **1a** through the reactor and periodically collect 1.5 mL or 10 mL fractions. The fractions were immediately concentrated or placed under a nitrogen atmosphere before concentration and then placed under vacuum. Purity was assessed by NMR and conversion was calculated. Time was plotted as a function of the mid-point of the collection period.

9. Reactor Setup for the β-borylation reaction

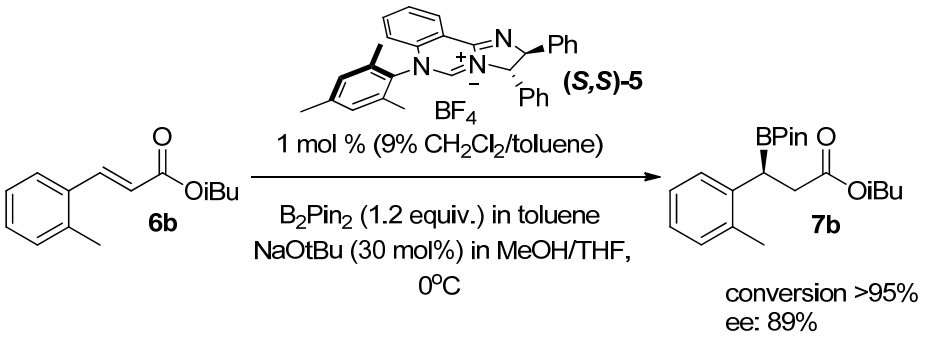
A) Reactor Configuration – Reactor view



Description from left to right (see figure 4.7 for picture): The first pump (A) was connected with 32 cm of drop tubing to the **bottom** of a glass Omnifit column (B) (6.6 mm diameter) containing 1.65 g of the copper (I) oxide/4Å molecular sieve (as outlined above) with a void volume ~1.6 mL. An additional 32 cm of tubing connected the **top** outlet of the column to a 100 psi backpressure regulator which was connected to one inlet on a 2.0 mL tube cooled reactor (E). A second pump (C) (with a 100 psi back pressure regulator placed in-line after the pump) was connected with 50 cm of drop tubing to a t-mixer where a third pump (D) with 50 cm of drop tubing was also connected. This reagent stream was connected to the second inlet of the 2 mL tube cooled reactor. Finally, an additional 20 cm of tubing connected the outlet of the coil to a 100 psi backpressure regulator and extra tubing to reach a fraction collector (F).



Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (7a): A solution of imidazolium salt **1a** (0.02M, 0.05 eq) in 80% CH_2Cl_2/ 20% toluene was prepared and pumped through *inlet A* at a rate of 0.800 mL/min. The salt flowed through the copper oxide (B) column. Upon exiting the resulting solution entered reactor E and was pre-cooled to 0ºC. A solution of α,β-unsaturated ester **6a** (0.4M, 1 eq) and bis(pinacolato) diboron (0.48 M, 1.2 eq) was prepared in toluene and pumped through *inlet C* at a rate of 0.800 mL/min. This was combined with a NaO^{t}Bu solution (0.6M, 0.30 eq prepared from a 2M in THF solution) in MeOH pumped from *inlet D* at 0.160 ml/min outside cooled reactor F at a t-mixer. The reagent and catalyst streams were mixed and allowed to react at 0ºC. Upon exiting 8 mL (theoretical 1.447 mmol) was collected, filtered through silica gel, washed with Et_2O, concentrated, and chromatographed with 5% EtOAc/ 95% hexanes to provide a volatile oil (276 mg, 79% yield) after brief drying under vacuum. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.12 (q, J=7.12 Hz, 2H), 2.43 (dd, J=16.4, 7.7, 1H), 2.36 (dd, J=16.4, 6.7 Hz, 1H), 1.37 (m, J=6.29 Hz, 1H), 1.26-1.22 (m, 16 H), 1.00 (d, J=7.50 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 83.1, 60.1, 37.7, 24.72, 24.66, 15.1, 14.3 ppm. The ^{1}H NMR and ^{13}C NMR data were in accordance with those described in the literature.[39]



Isobutyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(o-tolyl)propanoate (7b): These preliminary results were performed using a setup of ion exchange resin/ Cu_2O/ 4Å molecular sieve column and a 2 mL coil reactor. A solution of 6-NHC imidazoquinazolium salt **5** (0.004M, 0.01 eq) in 9% CH_2Cl_2/ 91% toluene was prepared and pumped through a column of ion exchange resin followed by copper oxide column with a residence time of 3 minutes in the copper oxide column. Upon exiting the resulting solution entered the coil reactor and was pre-cooled to 0ºC. A solution of α,β-unsaturated ester **6b** (0.4M, 1 eq) and bis(pinacolato) diboron (0.48 M, 1.2 eq) was prepared in toluene combined with a separate solution of NaOtBu (0.6M, 0.30 eq) in MeOH (prepared using a 2M NaOtBu in THF solution) prior to entering the coil reactor. The reagent and catalyst streams reacted at 0ºC and upon exiting a sample was taken and analyzed by GC indicating >95% conversion to known product **7b**. Upon oxidation with NaOH and peroxide 89% ee was determined by chiral GC with comparison to previously obtained spectrum.[39]

See Appendix 3 for copies of ^{1}H and ^{13}C NMR spectra.

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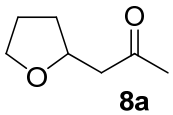
APPENDIX 1

Supporting Information for Chapter 2

1. Chromatograms of Racemic and Enantiomerically Enriched Products

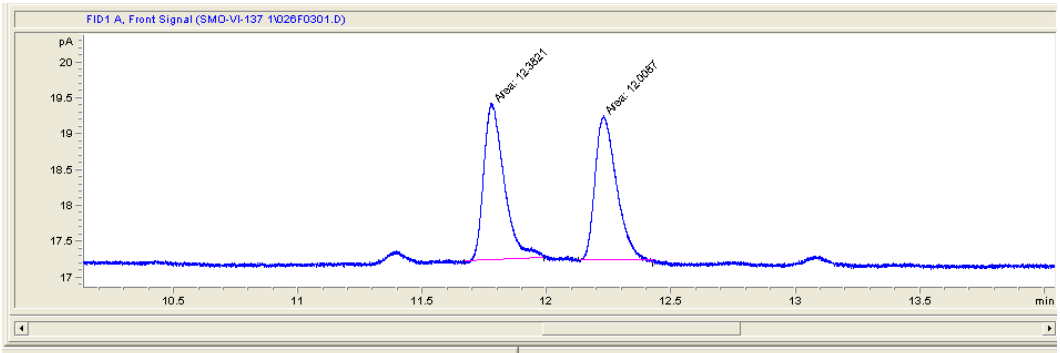
* Note: Racemic compounds were synthesized by exposure of starting materials to racemic D,L proline.



8a

Method: Chiraldex B-DM capillary column (30m x 0.25 mm x 0.12µm film thickness) 85°C hold 15 min constant flow of 1.6205 ml/min.

Racemic



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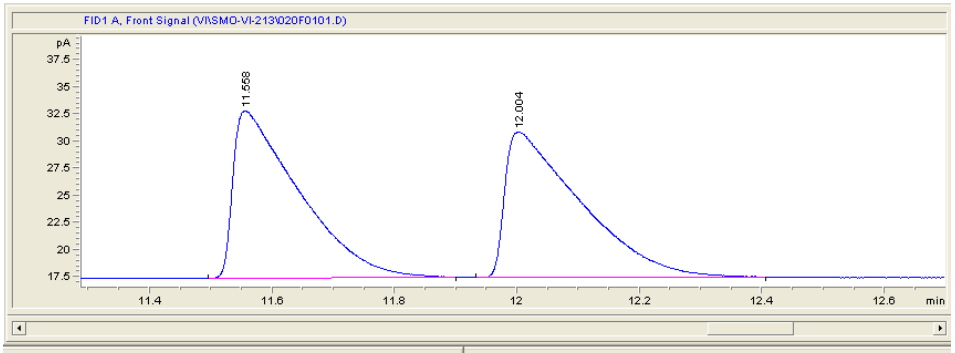
Sample Info	
Barcode	
Operator	jkp
Method	85C HOLD 20.M

#	Time	Area	Height	Width	Area%	Symmetry
1	11.778	12.4	2.2	0.0953	50.766	0.605
2	12.227	12	2	0.0999	49.234	0.661

Enantioenriched: 0% ee



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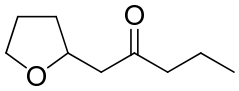
Sample Info	
Barcode	
Operator	jkp
Method	K1- 85C HOLD 15MIN.M

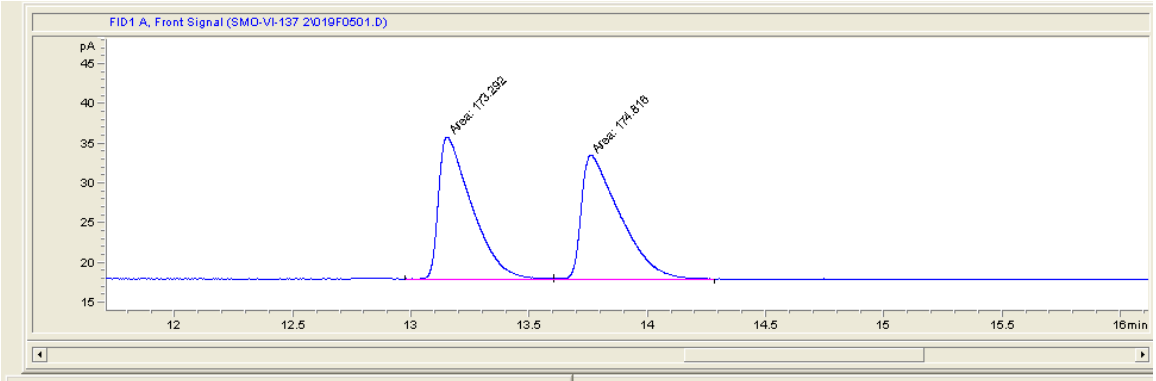
#	Time	Area	Height	Width	Area%
1	11.558	115	15.4	0.0967	50.112
2	12.004	114.5	13.4	0.1125	49.888



8b

Method: Chiraldex B-DM capillary column (30m x 0.25 mm x 0.12µm film thickness) 90°C hold 20 min constant flow of 4.2 ml/min.

Racemic



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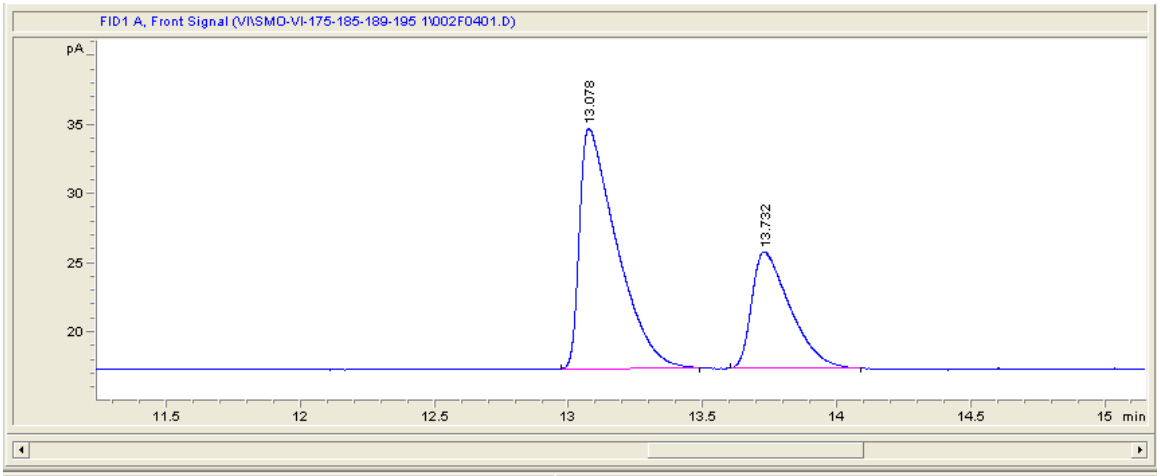
Barcode	
Operator	jkp
Method	USE_90C HOLD 20_200 SPLIT 4_2ML-MIN.M

#	Time	Area	Height	Width	Area%	Symmetry
1	13.148	173.3	17.9	0.1615	49.781	0.324
2	13.757	174.8	15.5	0.1878	50.219	0.318

Enantioenriched: 33% ee



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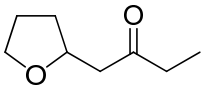
Sample	SMO-VI-175 P3
Sample Info	
Barcode	
Operator	jkp
Method	K3_90C HOLD 20_200 SPLIT 4_2ML-MIN.M

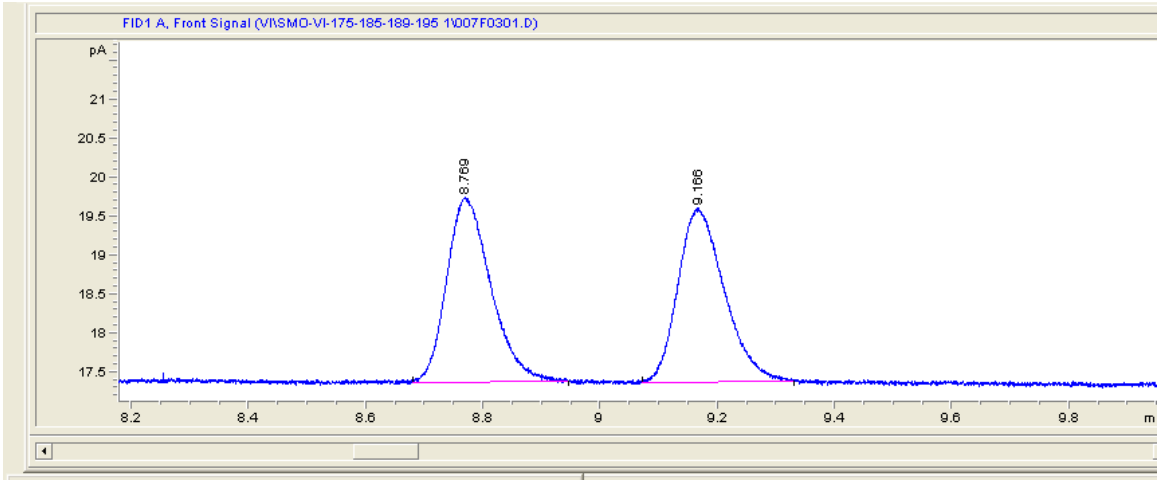
#	Time	Area	Height	Width	Area%	Sy
1	13.078	167.7	17.4	0.1302	66.629	
2	13.732	84	8.4	0.1342	33.371	



8c

Method: Chiraldex B-DM capillary column (30m x 0.25 mm x 0.12µm film thickness). 88°C hold 30 min constant flow of 4.2ml/min.

Racemic



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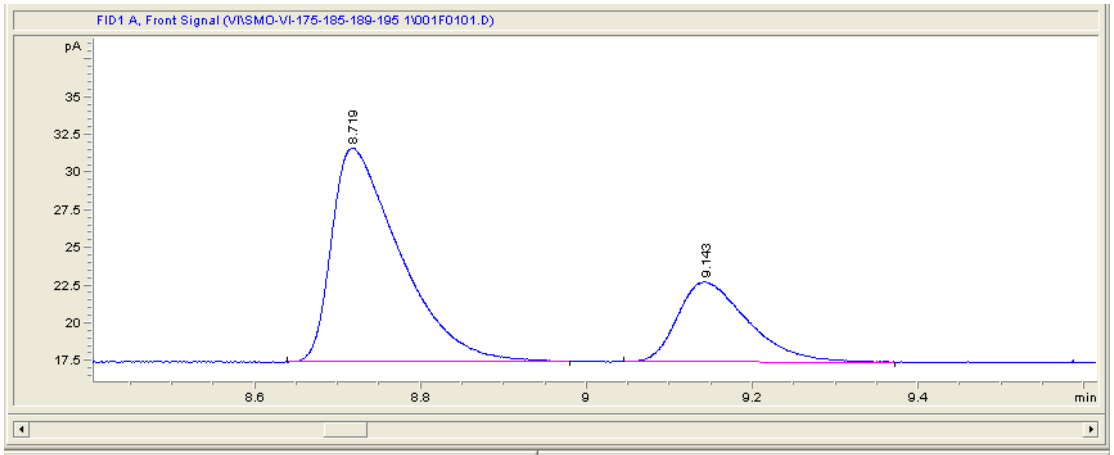
Date	16-Sep-10, 12:27:40
Sample	SMO-VI-P2 rac
Sample Info	
Barcode	
Operator	jkp
Method	88C HOLD 30_200 SPLIT 4_2ML-MIN.M

#	Time	Area	Height	Width	Area%
1	8.769	12.4	2.4	0.0757	50.274
2	9.166	12.2	2.2	0.0795	49.726

Enantioenriched: 44% ee



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Date	16-Sep-10, 11:24:39
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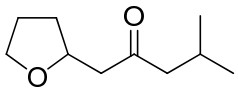
Sample Info	
Barcode	
Operator	jkp
Method	88C HOLD 30_200 SPLIT 4_2ML-MIN.M

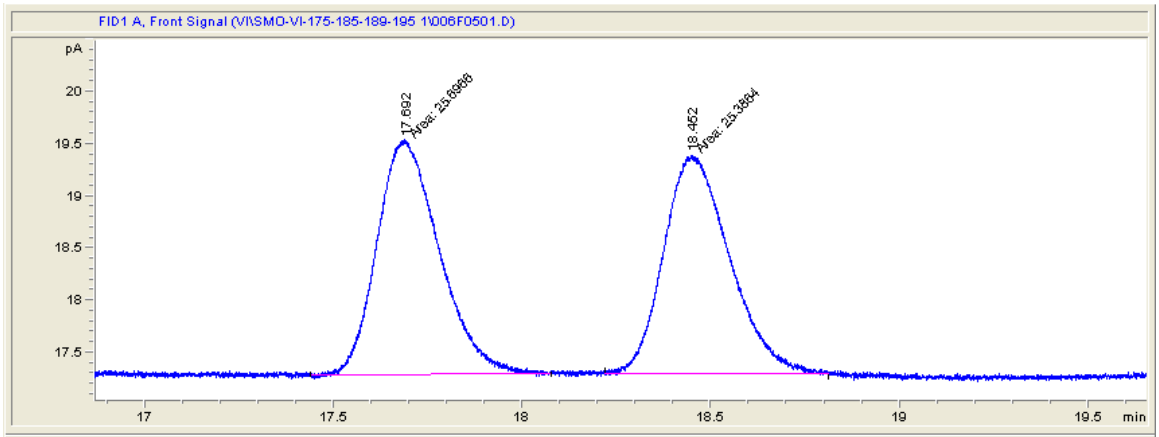
#	Time	Area	Height	Width	Area%	Sy
1	8.719	80.9	14.1	0.0827	72.268	
2	9.143	31.1	5.3	0.0878	27.732	



8d

Method: Chiraldex B-DM capillary column (30m x 0.25 mm x 0.12µm film thickness) 90°C hold 20 min constant flow of 4.2 ml/min.

Racemic



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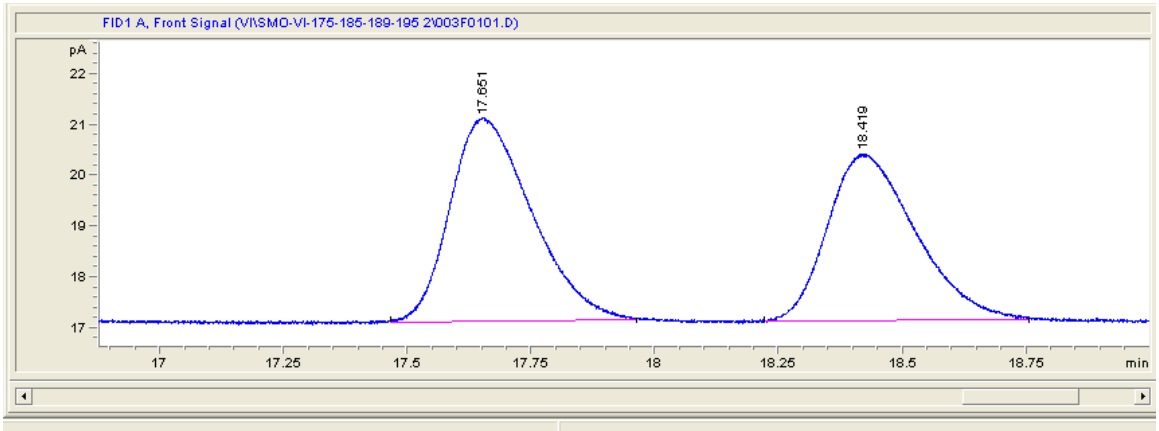
Sample Info	
Barcode	
Operator	jkp
Method	K3_90C HOLD 20_200 SPLIT 4_2ML-MIN.M

#	Time	Area	Height	Width	Area%	Sy
1	17.692	25.7	2.2	0.1917	50.304	
2	18.452	25.4	2.1	0.2029	49.696	

Enantioenriched: 6% ee



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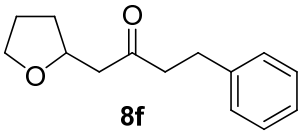
Method	K3_90C HOLD 20_200 SPLIT 4_2ML-MIN.M

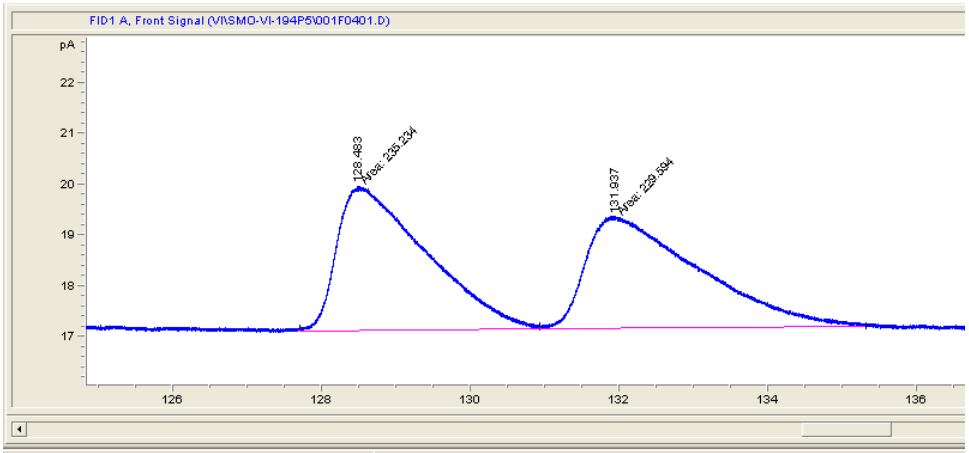
#	Time	Area	Height	Width	Area%	Sy
1	17.651	45.7	4	0.1371	53.105	
2	18.419	40.3	3.3	0.1485	46.895	



8f

Method: Chiraldex B-DM capillary column. 120°C hold 180 min constant flow of 2.5 ml/min.

Racemic:



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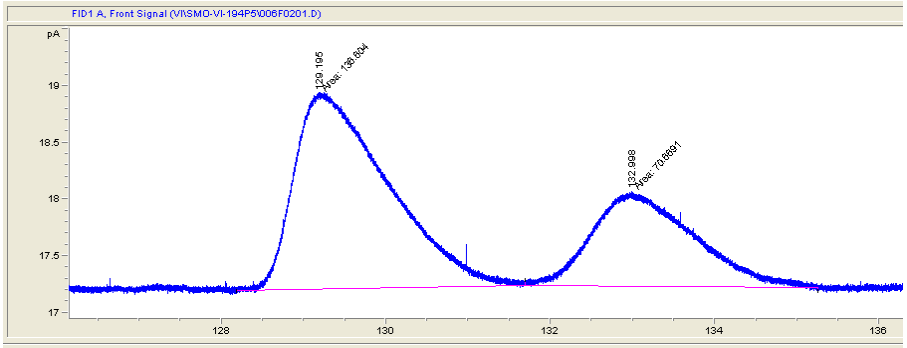
Sample Info	
Barcode	
Operator	jkp
Method	120C HOLD 180_2=5 ML-MIN.M

#	Time	Area	Height	Width	Area%	Symmetry
1	128.483	235.2	2.8	1.3855	50.607	0.31
2	131.937	229.6	2.2	1.7497	49.393	0.328

Enantioenriched: 32% ee



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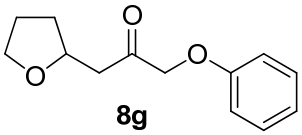
Sample Info	
Barcode	
Operator	jkp
Method	120C HOLD 180_2=5 ML-MIN.M

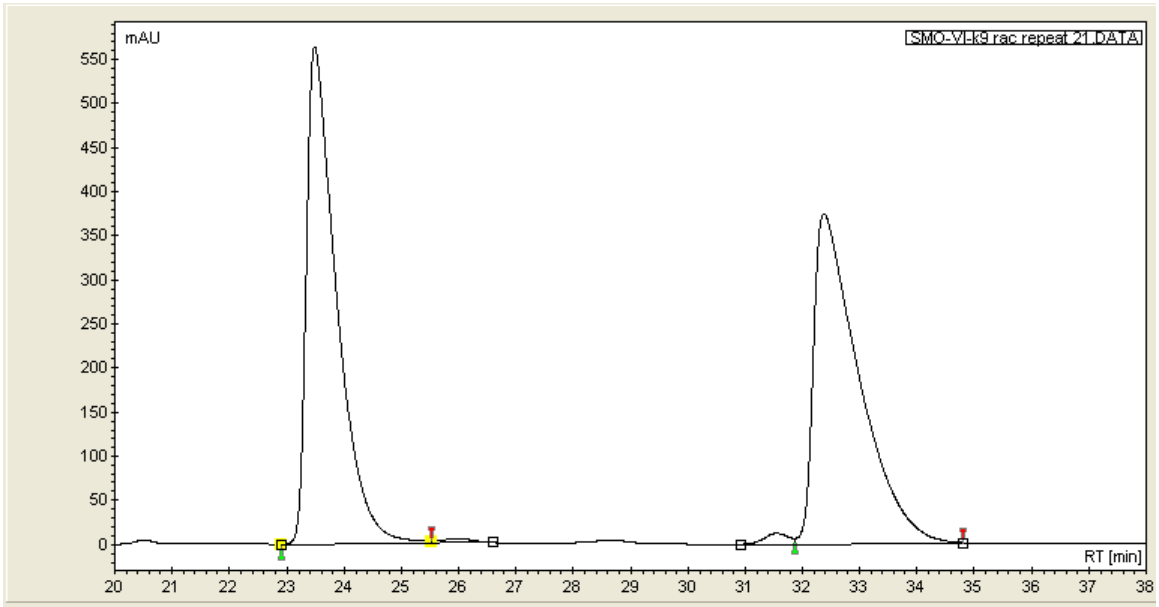
#	Time	Area	Height	Width	Area%	Symmetry
1	129.195	136.6	1.7	1.319	65.905	0.37
2	132.998	70.7	8.4E-1	1.4048	34.095	0.633



8g

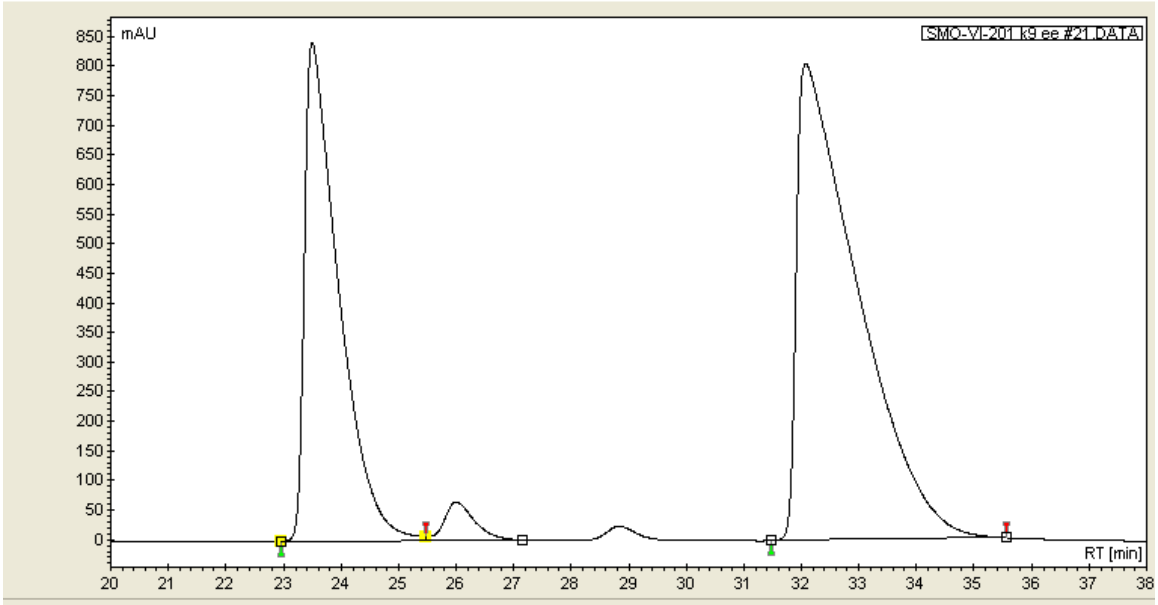
Method: CHIRALPAK IB and guard column 99% hex 1% IPA 1.0 ml/min, 220 nm

Racemic

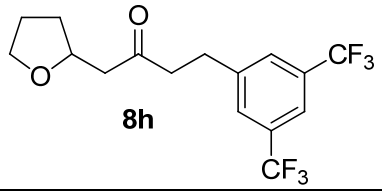


#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23.49	50.12	563.9	343.7	50.121
2	UNKNOWN	32.37	49.88	374.1	342.0	49.879

Enantioenriched: 26% ee



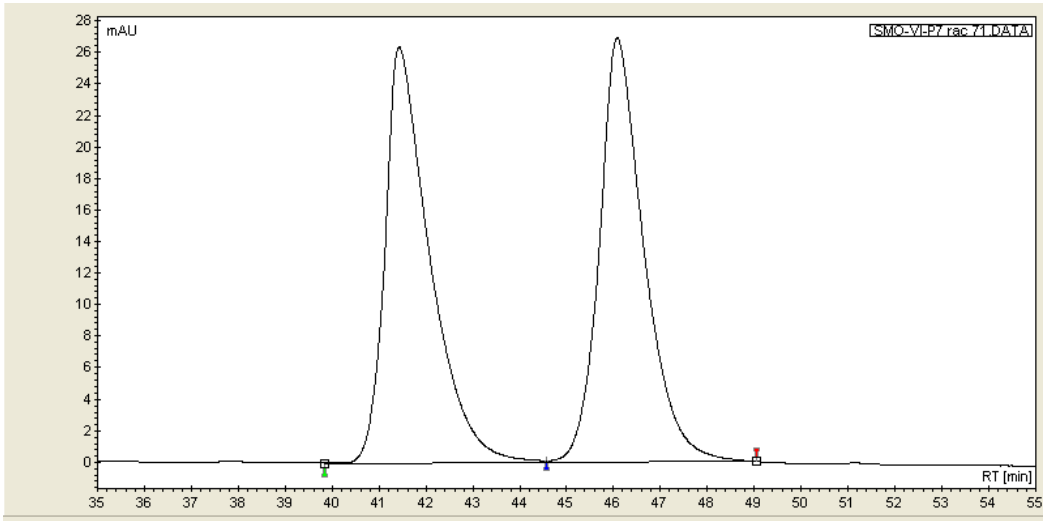
#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23.50	36.95	842.0	581.3	36.949
2	UNKNOWN	32.07	63.05	805.1	992.0	63.051



8h

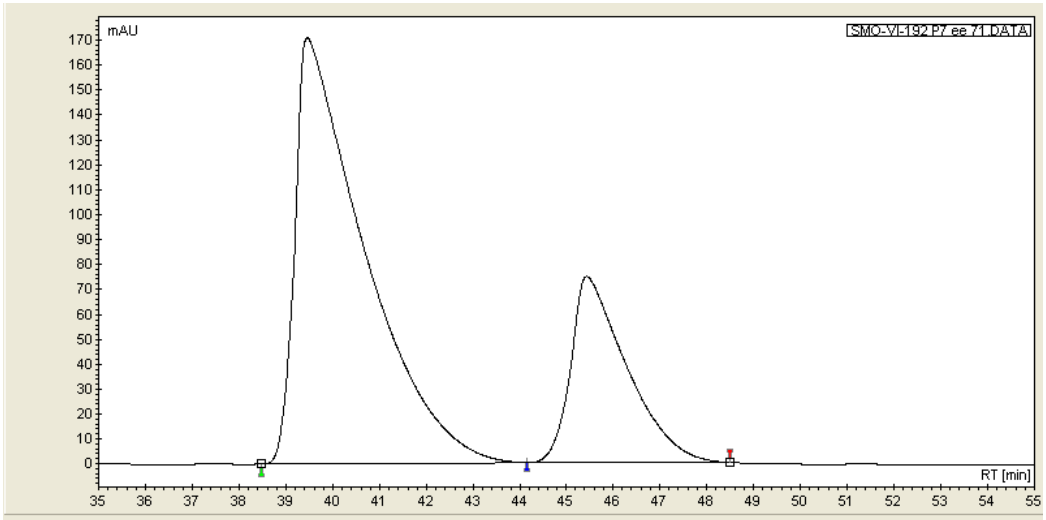
Method: CHIRALPAK IA and guard column 20% (of a 1% IPA solution in pentane) 80% pentane 0.5 ml/min 220nm

Racemic

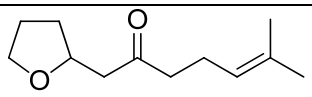


#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	41.43	49.60	26.4	29.2	49.600
2	UNKNOWN	46.08	50.40	26.9	29.6	50.400
Total			100.00	53.3	58.8	100.000

Enantioenriched: 48% ee



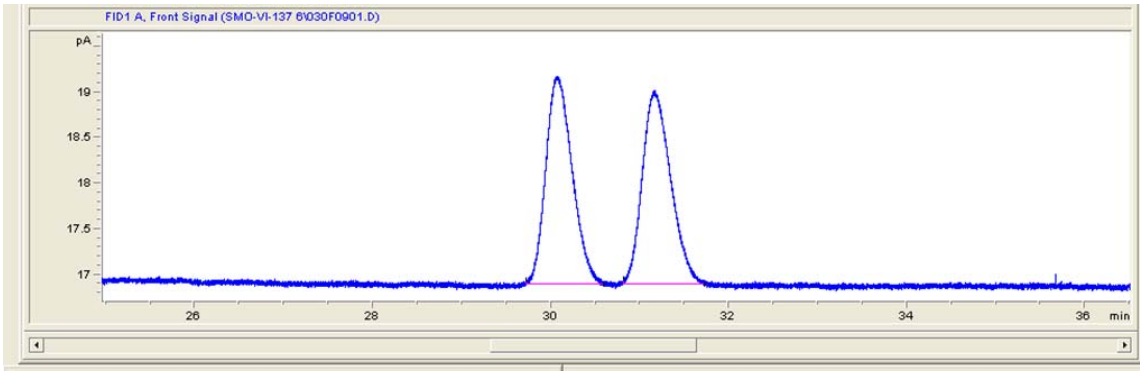
#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	39.46	73.92	170.7	292.9	73.923
2	UNKNOWN	45.43	26.08	74.7	103.3	26.077
Total			100.00	245.5	396.3	100.000



8i

Method: Chiraldex B-DM capillary column. 110°C hold 60 min constant flow of 4.2 ml/min

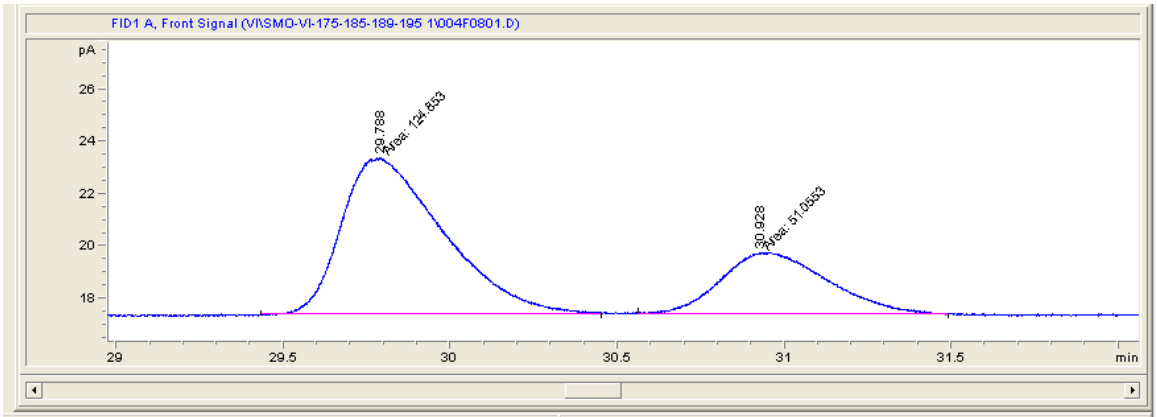
Racemic



File Information	
GC-File	030F0901.D
File Path	C:\CHEM32\2\DATA\SMO\SMO-VI-137 6\
Date	17-Aug-10, 03:09:13
Sample	SMO-VI-137 K10 rac #8
Sample Info	
Barcode	
Operator	jkp
Method	110 HOLD 60_100 SPLIT 4_2ML-MIN.M

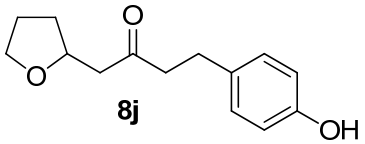
#	Time	Area	Height	Width	Area%	Symmetry
1	30.07	46.8	2.3	0.2423	50.132	0.737
2	31.171	46.6	2.1	0.2609	49.868	0.792

Enantioenriched: 42% ee



File Information	
GC-File	004F0801.D
File Path	C:\CHEM32\2\DATA\SMO\VI\SMO-VI-175-185-189-195 1\
Date	16-Sep-10, 15:46:26
Sample	SMO-VI-195 P10 200 split
Sample Info	
Barcode	
Operator	jkp
Method	K10 110 HOLD 60_200SPLIT 4_2ML-MIN.M

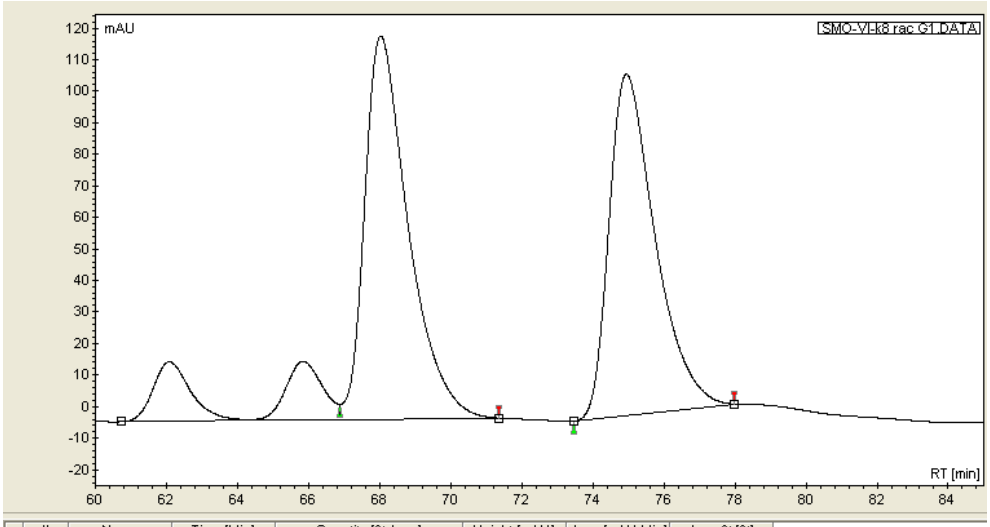
#	Time	Area	Height	Width	Area%	Sy
1	29.788	124.9	5.9	0.3498	70.976	
2	30.928	51.1	2.3	0.3636	29.024	



8j

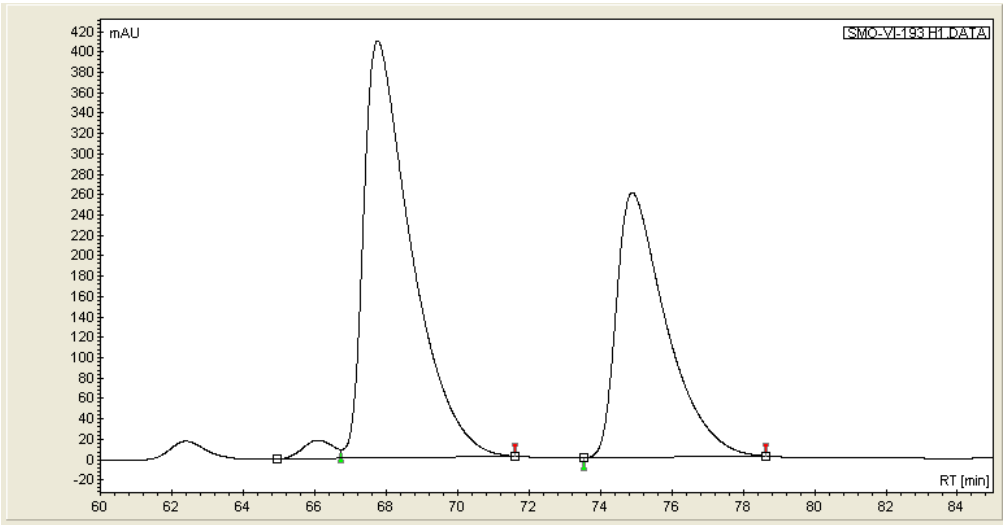
Method: CHIRALPAK IB column and guard column 92% Hexane 8% IPA 0.3 ml/min 220 nm

Racemic

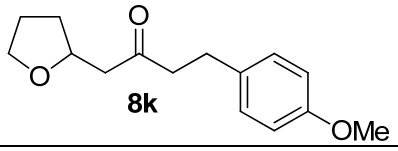


#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	68.03	51.53	121.5	172.8	51.526
2	UNKNOWN	74.94	48.47	108.2	162.6	48.474
Total			100.00	229.7	335.4	100.000

Enantioenriched: 20% ee



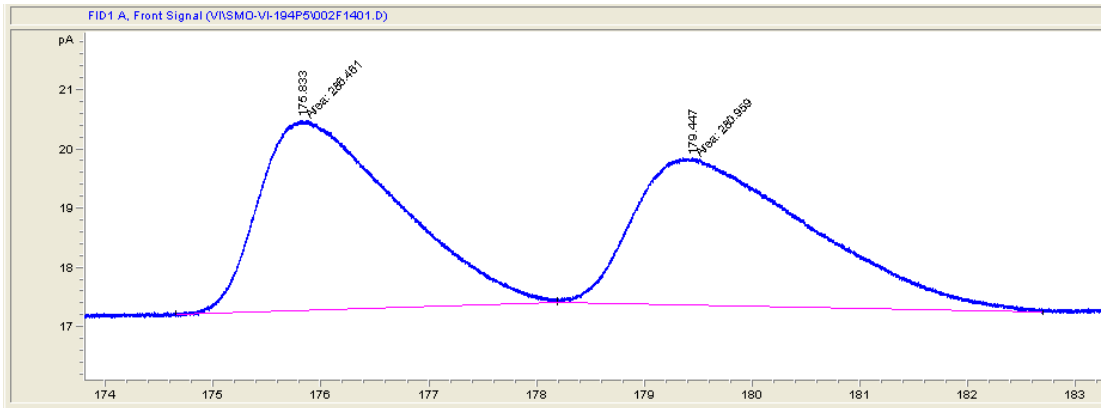
#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	67.76	60.10	409.5	631.9	60.103
2	UNKNOWN	74.89	39.90	260.0	419.4	39.897



8k

Method: Chiraldex B-DM capillary column. 120°C hold 10 min, ramp at 5°C/min to 140°C hold 180min, constant flow of 2.0 ml/min.

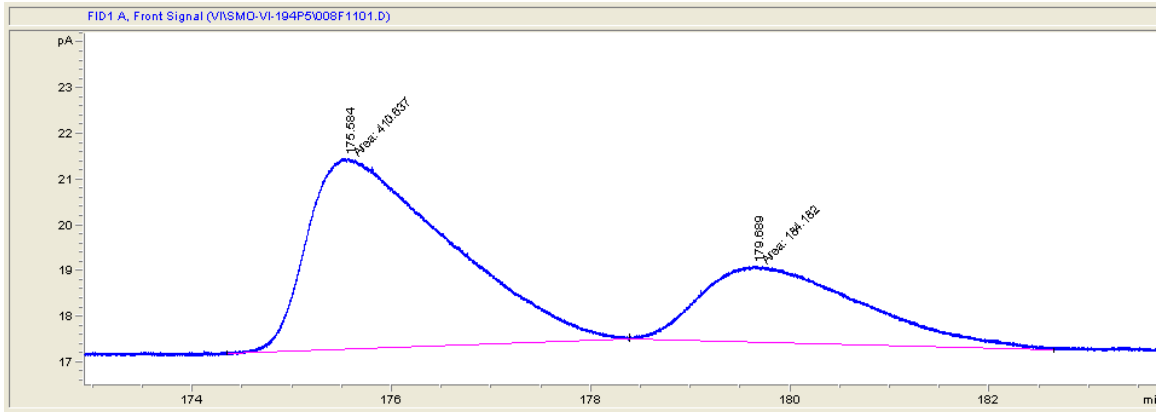
Racemic



File Information	
GC-File	002F1401.D
File Path	C:\CHEM32\2\DATA\SMO\VI\SMO-VI-194P5\
Date	16-Dec-10, 05:18:06
Sample	SMO-VI-P6 rac
Sample Info	
Barcode	
Operator	jkp
Method	120-140C RATE 5HOLD 190_2=0 ML-MIN.M

#	Time	Area	Height	Width	Area%	Symmetry
1	175.833	286.5	3.2	1.4894	50.485	0.451
2	179.447	281	2.5	1.8969	49.515	0.363

Enantioenriched: 38% ee

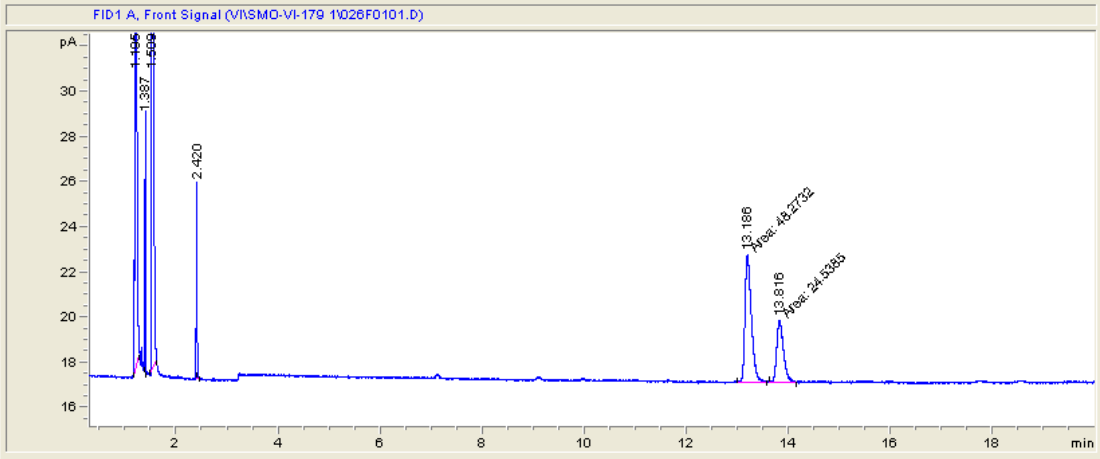


File Information	
GC-File	008F1101.D
File Path	C:\CHEM32\2\DATA\SMO\VI\SMO-VI-194P5\
Date	16-Dec-10, 01:53:31
Sample	SMO-VI-196 P6
Sample Info	
Barcode	
Operator	jkp
Method	120-140C RATE 5HOLD 190_2=0 ML-MIN.M

#	Time	Area	Height	Width	Area%	Symmetry
1	175.584	410.6	4.2	1.6375	69.036	0.411
2	179.689	184.2	1.6	1.8615	30.964	0.537

2. Chiral GC traces of crude reaction mixtures for experiments in Table 5: Influence of Catalyst(s) on Enantiomeric Excess of 8b.

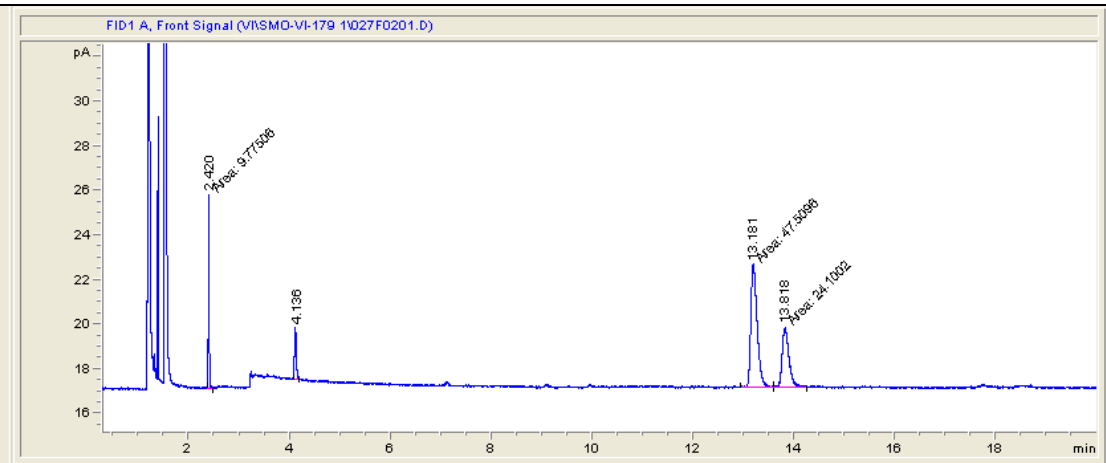
Product **8b** and OTBDPS-proline **2a**



File Information	
GC-File	026F0101.D
File Path	C:\CHEM32\2\DATA\SMO\VI\SMO-VI-179 1\
Date	09-Sep-10, 08:29:46
Sample	SMO-VI-179 A=36 hrs
Sample Info	
Barcode	
Operator	jkp
Method	K3_90C HOLD 20_200 SPLIT 4_2ML-MIN.M

#	Time	Area	Height	Width	Symmetry
1	1.195	11012	13921.5	0.0108	0.497
2	1.387	6.8	11.3	0.0102	0.955
3	1.509	1467.9	975.7	0.02	0.236
4	2.42	9.8	8.7	0.0172	0.873
5	13.186	48.3	5.6	0.1435	0.615
6	13.816	24.5	2.7	0.1518	0.715

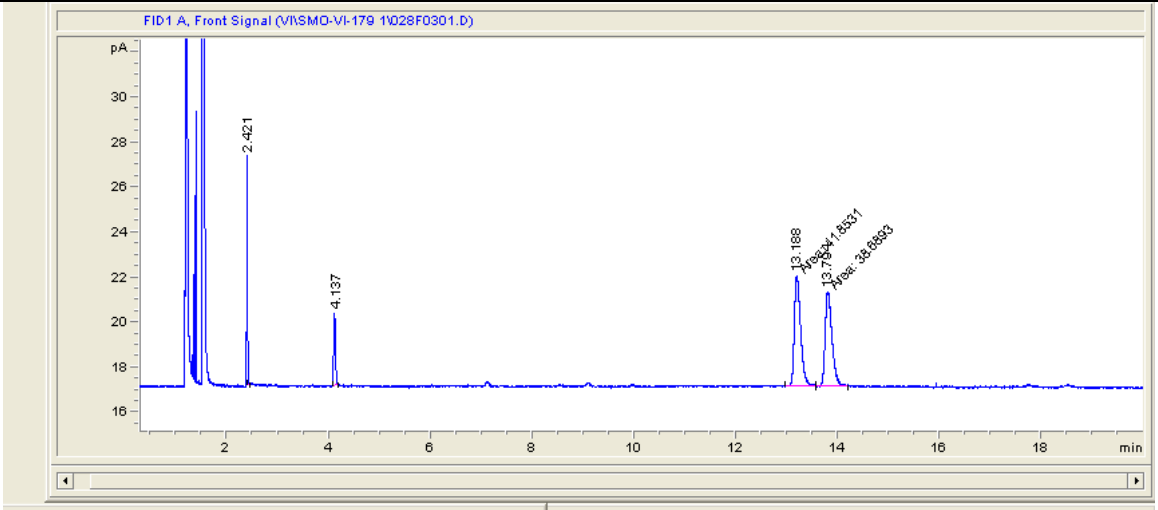
Product **8b** and Thiourea **1f**



File Information	
GC-File	027F0201.D
File Path	C:\CHEM32\2\DATA\SMO\VI\SMO-VI-179 1\
Date	09-Sep-10, 08:51:16
Sample	SMO-VI-179 B=36 hrs
Sample Info	
Barcode	
Operator	jkp
Method	K3_90C HOLD 20_200 SPLIT 4_2ML-MIN.M

#	Time	Area	Height	Width	Symmetry
1	2.42	9.8	8.7	0.0188	0.809
2	4.136	5.7	2.3	0.0381	0.822
3	13.181	47.5	5.5	0.145	0.518
4	13.818	24.1	2.6	0.1527	0.761

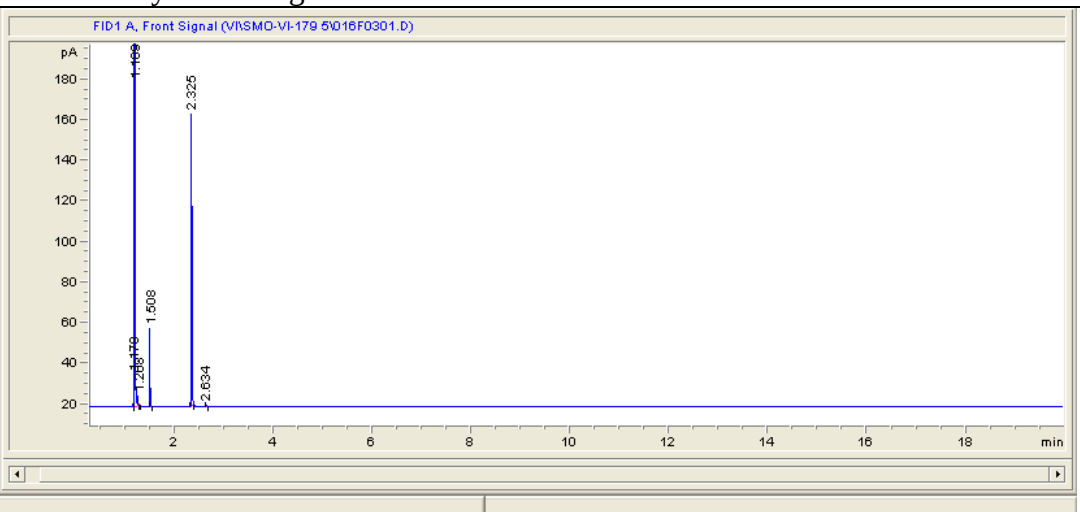
Product **8b** and OTBDPS-proline **2a** + thiourea **1f**



File Information	
GC-File	028F0301.D
File Path	C:\CHEM32\2\DATA\SMO\VI\SMO-VI-179 1\
Date	09-Sep-10, 09:12:42
Sample	SMO-VI-179 C = 36 hrs
Sample Info	
Barcode	
Operator	jkp
Method	K3_90C HOLD 20_200 SPLIT 4_2ML-MIN.M

#	Time	Area	Height	Width	Symmetry
1	2.421	11.3	10.1	0.0178	0.876
2	4.137	8	3.2	0.0388	0.824
3	13.188	41.9	4.9	0.1427	0.594
4	13.794	38.7	4.2	0.1542	0.526

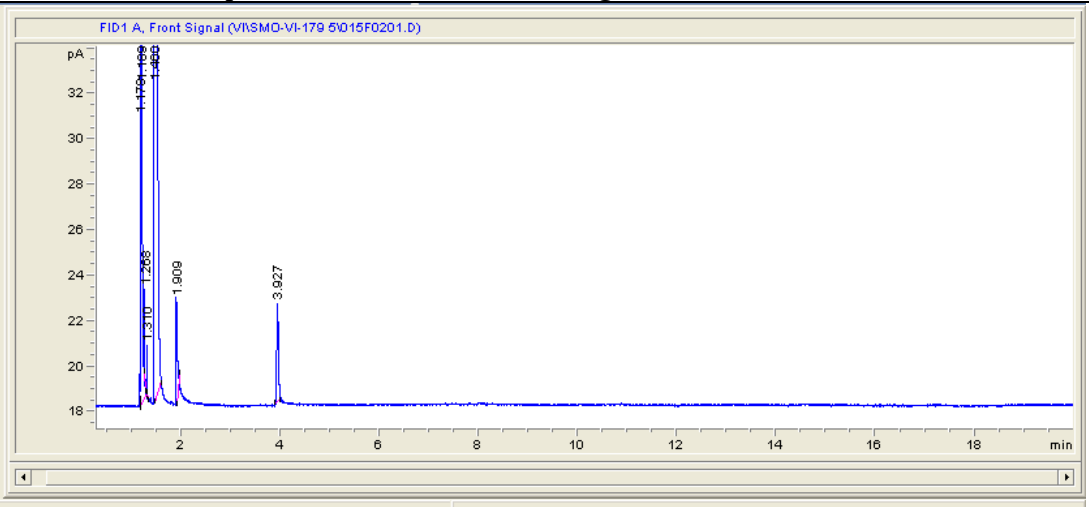
CG trace of mesitylene background



File Information	
GC-File	016F0301.D
File Path	C:\CHEM32\2\DATA\SMO\VI\SMO-VI-179 5\
Date	01-Jun-11, 13:22:01
Sample	mesitylene
Sample Info	
Barcode	
Operator	bao
Method	K3_90C HOLD 20_200 SPLIT 4_2ML-MIN.M

#	Time	Area	Height	Width	Symmetry
1	1.178	4.1	15.2	4.356E-3	1.051
2	1.189	11201.1	18009.1	0.0104	0.313
3	1.268	2.7	4.2	0.0101	0.804
4	1.508	24	38.4	9.8845E-3	0.771
5	2.325	156.2	144	0.0167	0.667
6	2.634	8.8E-1	7.2E-1	0.0176	0.902

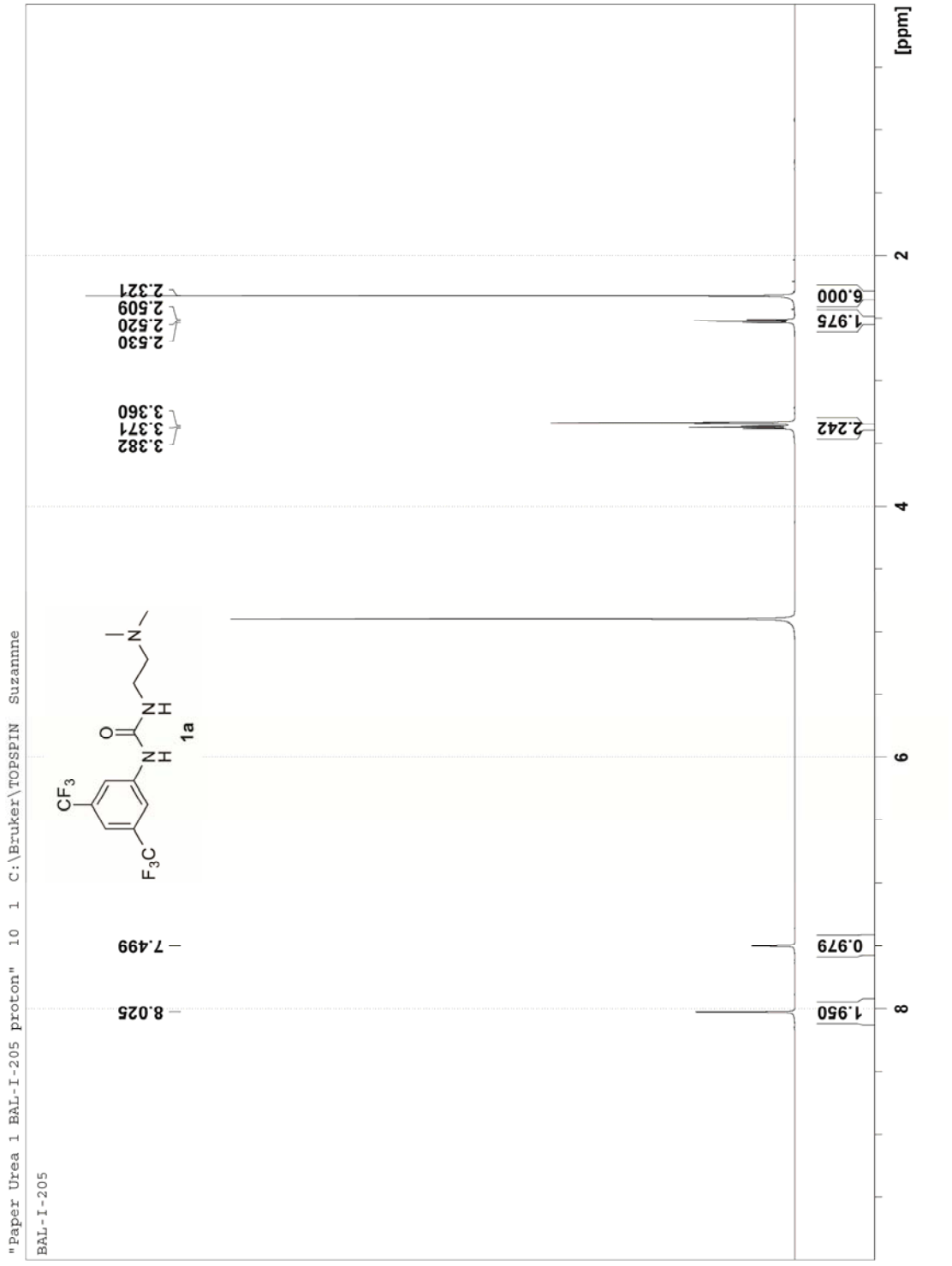
GC trace of OTBDPS-proline **2a** + thiourea **1f** background

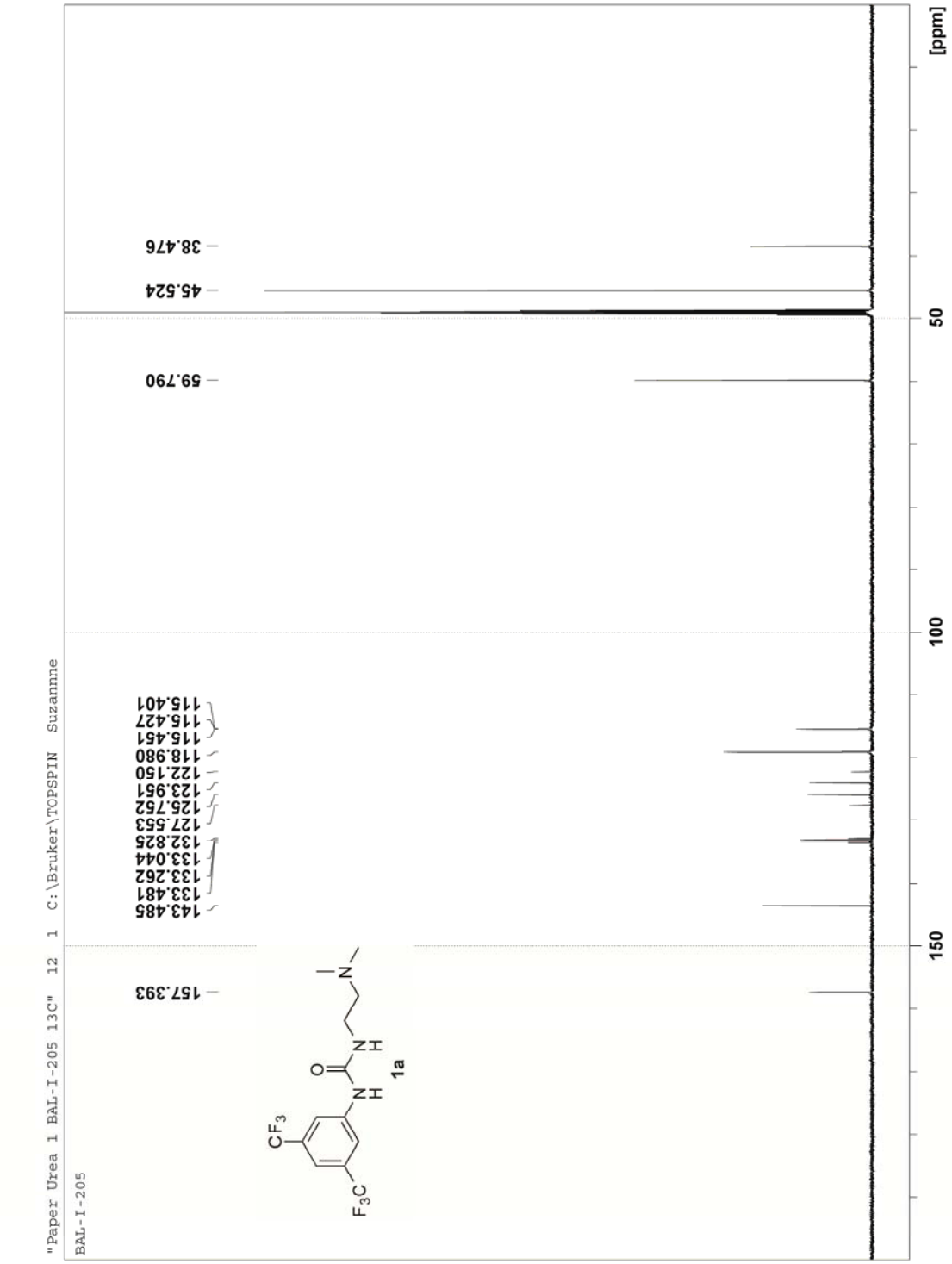


File Information	
GC-File	015F0201.D
File Path	C:\CHEM32\2\DATA\SMO\VI\SMO-VI-179 5\
Date	01-Jun-11, 13:00:14
Sample	OTBDPS proline + thiourea background
Sample Info	
Barcode	
Operator	bao
Method	K3_90C HOLD 20_200 SPLIT 4_2ML-MIN.M

#	Time	Area	Height	Width	Area%	Symmetry
1	1.178	3.5	12.7	4.4413E-3	0.027	1.042
2	1.189	9704.5	16278	9.9361E-3	75.309	0.327
3	1.268	2.3	4.1	8.901E-3	0.018	0.859
4	1.31	1.1	2.2	7.9029E-3	0.008	0.998
5	1.46	3158.8	1724.7	0.023	24.513	9.55E-2
6	1.909	5.5	4.5	0.0168	0.043	0.144
7	3.927	10.5	4.3	0.0378	0.082	0.791

2. ^{1}H and ^{13}C NMR Spectra of Chemical Compounds

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133.481
133.262
133.044
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50
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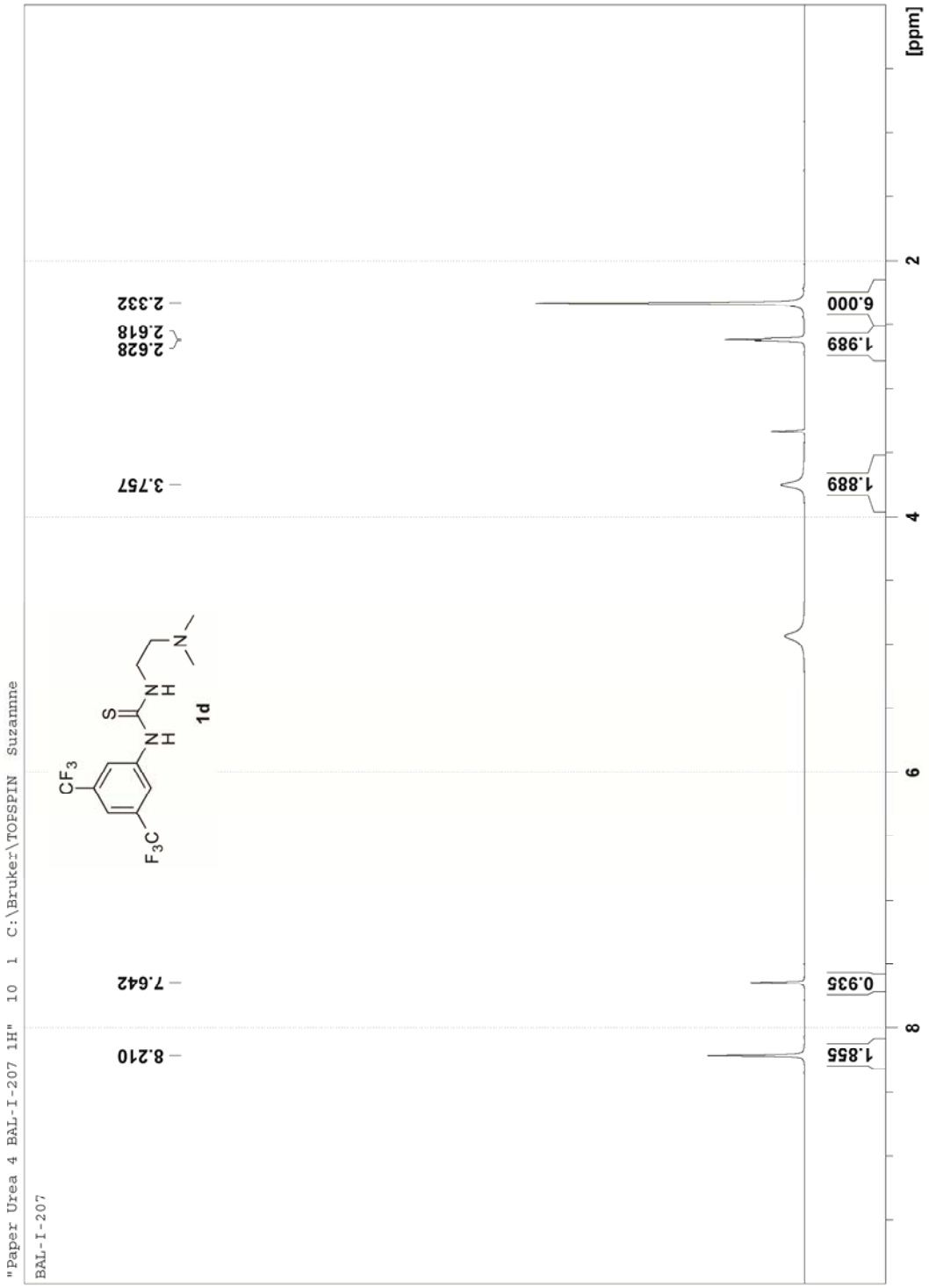
150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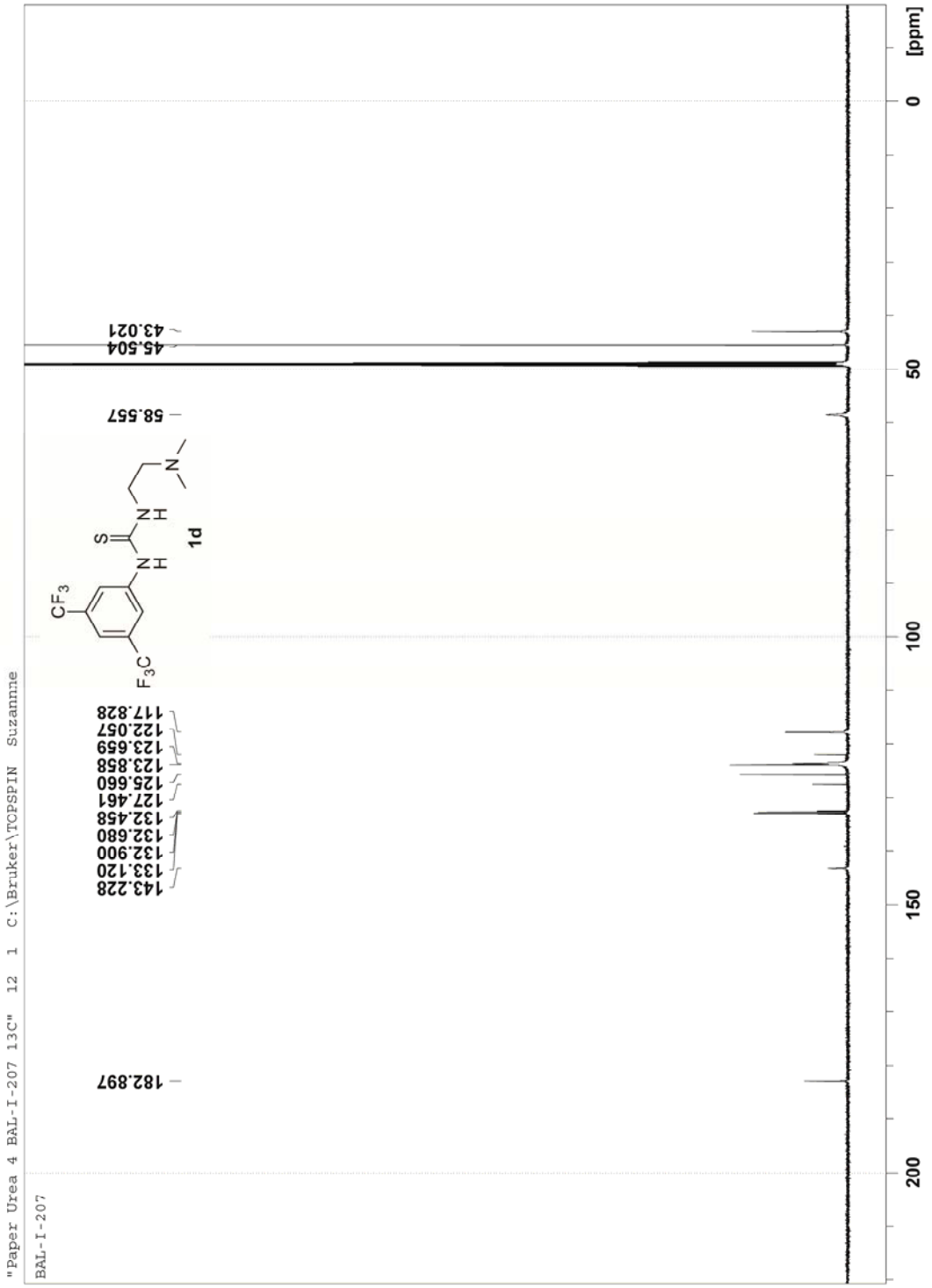
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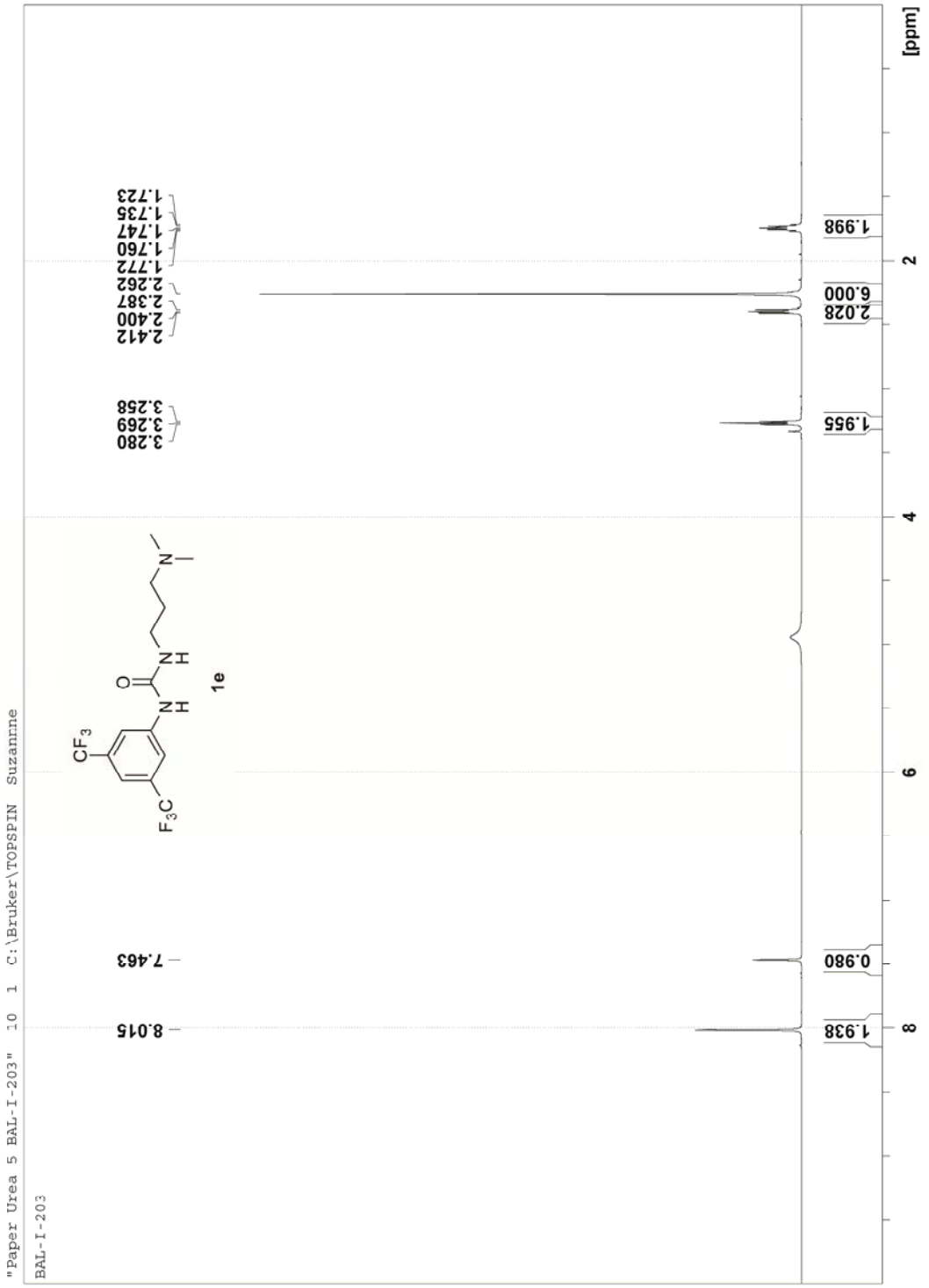
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2.262
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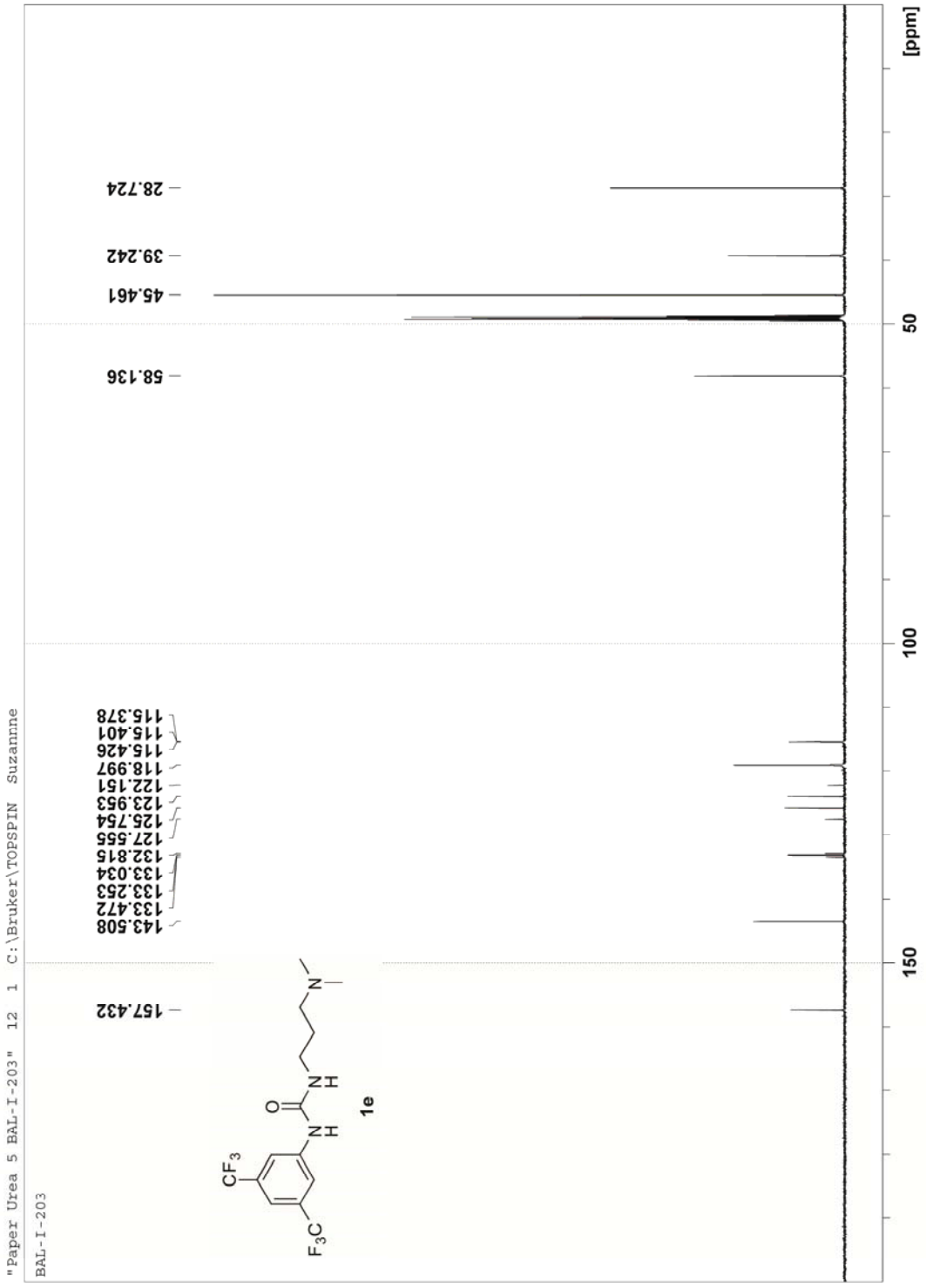
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125.754
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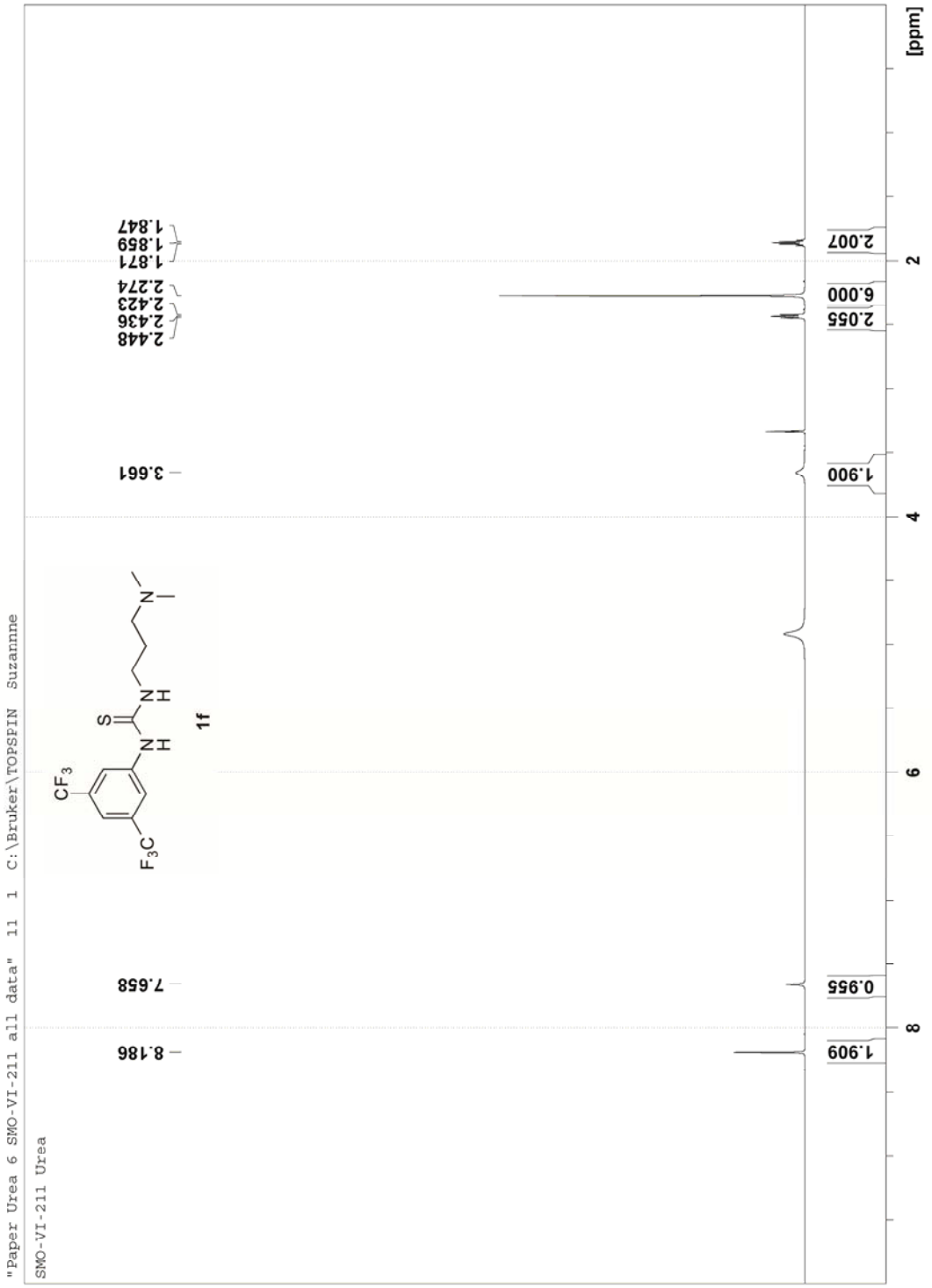
150
100
50
[ppm]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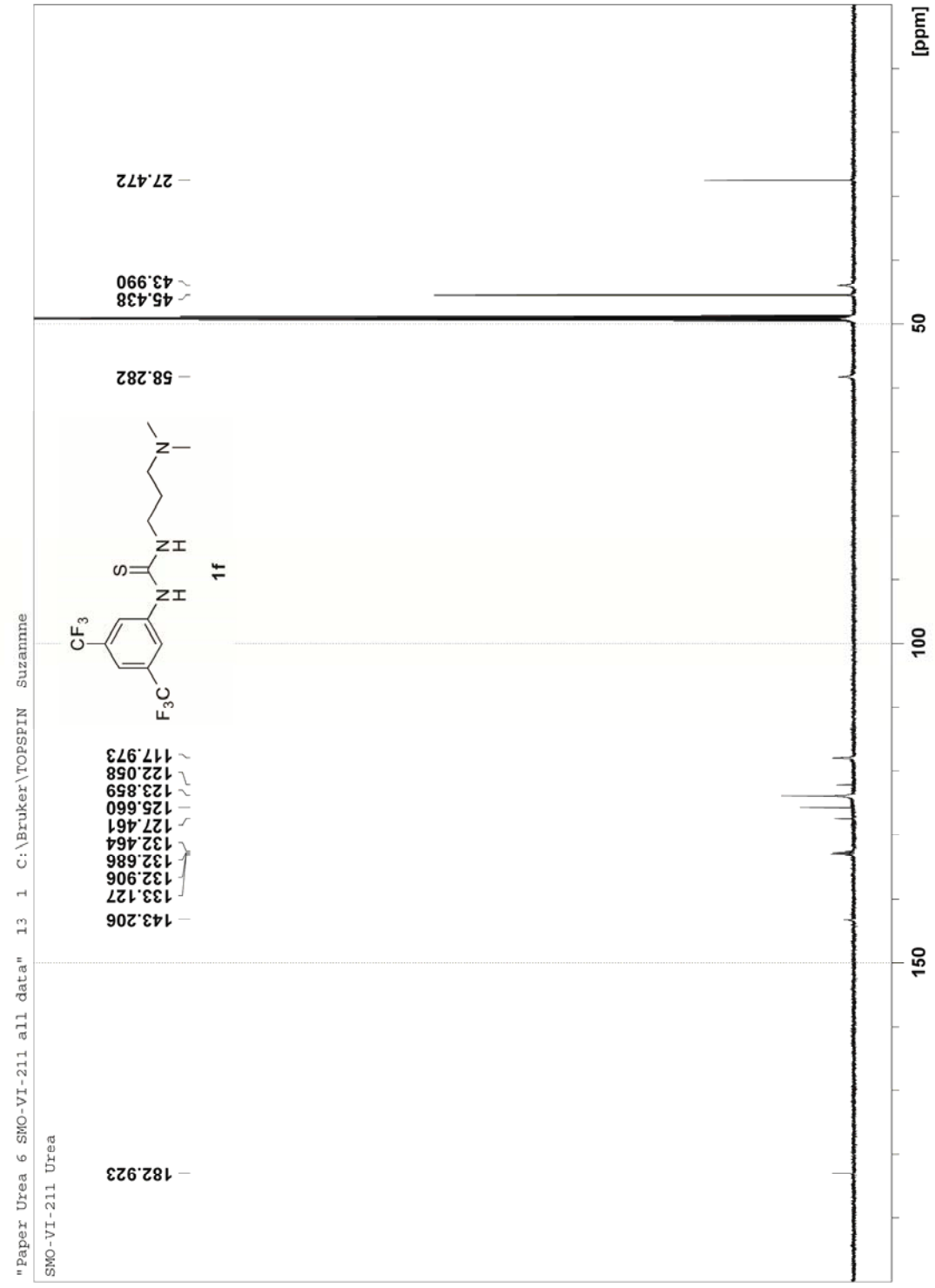
[ppm]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132.464
127.461
125.660
123.859
122.058
117.973
58.282
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H
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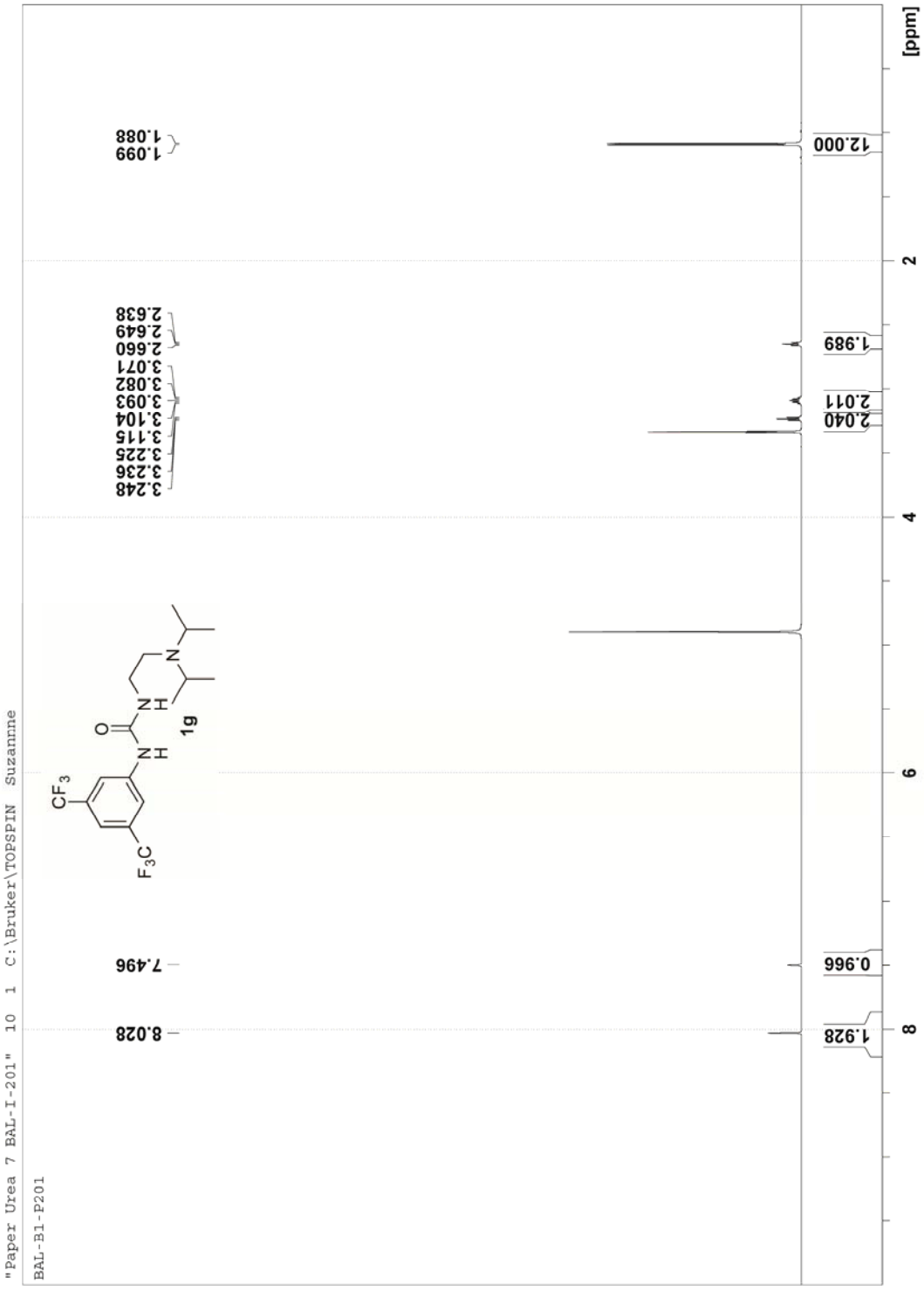
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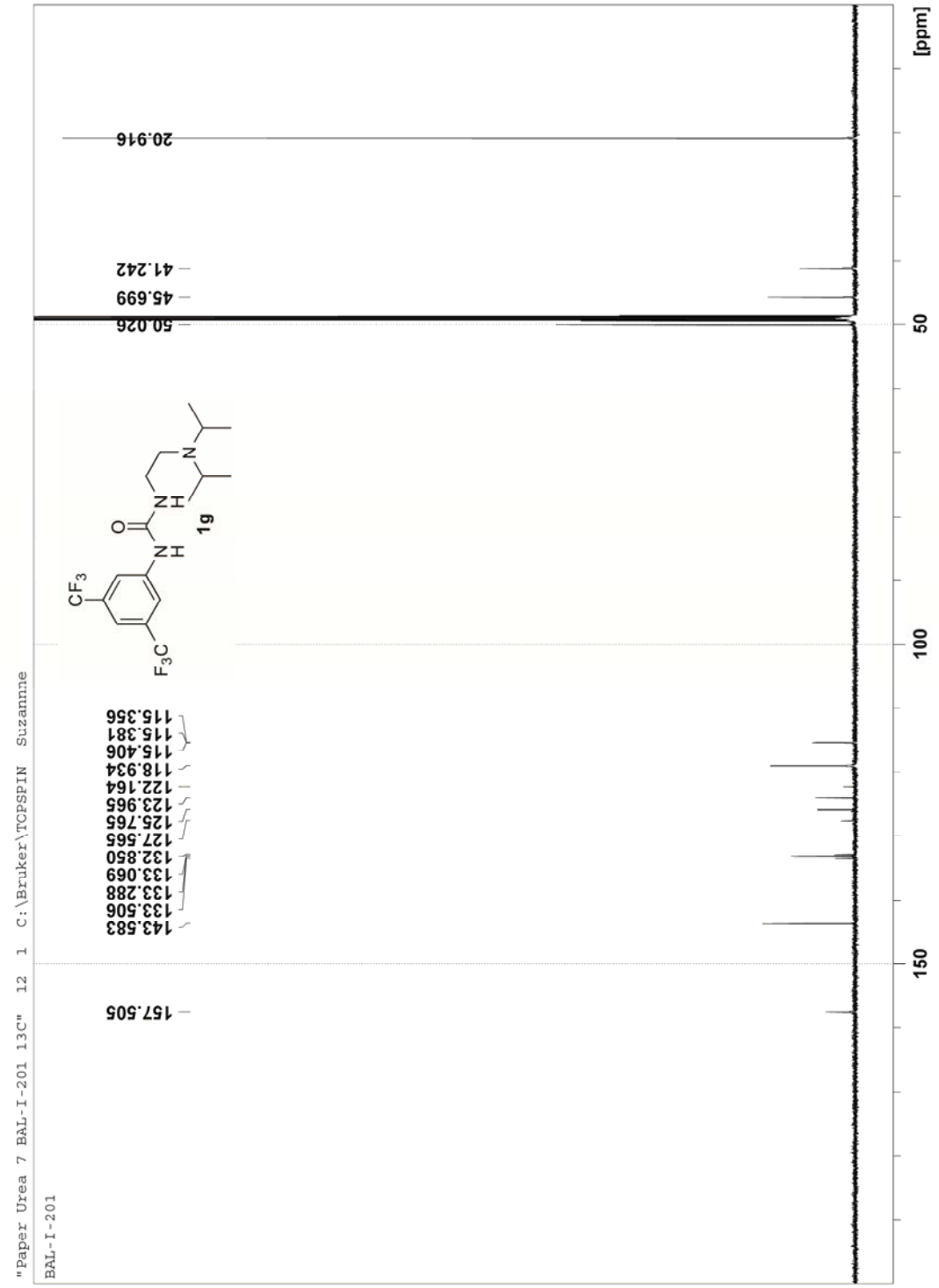
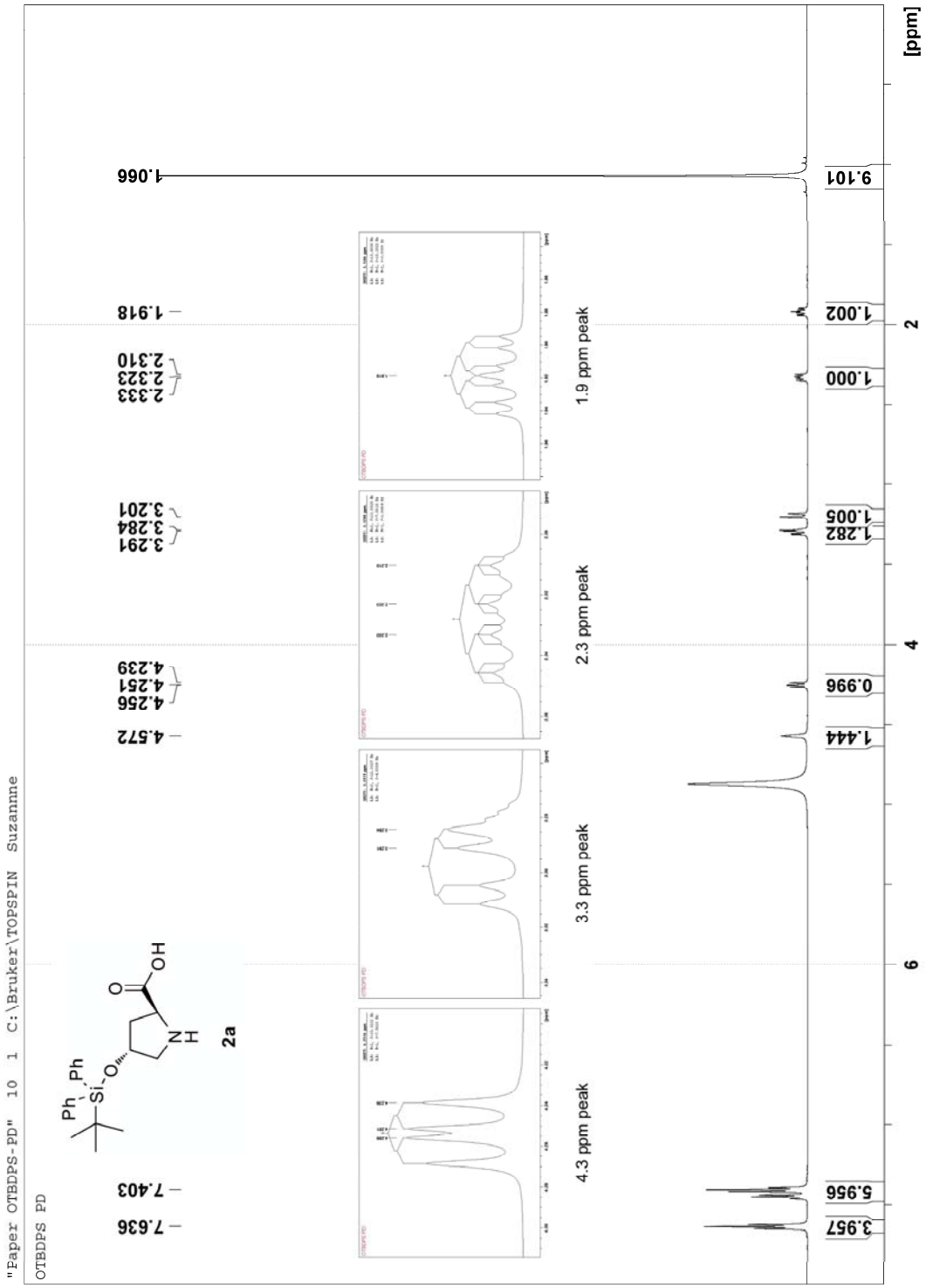
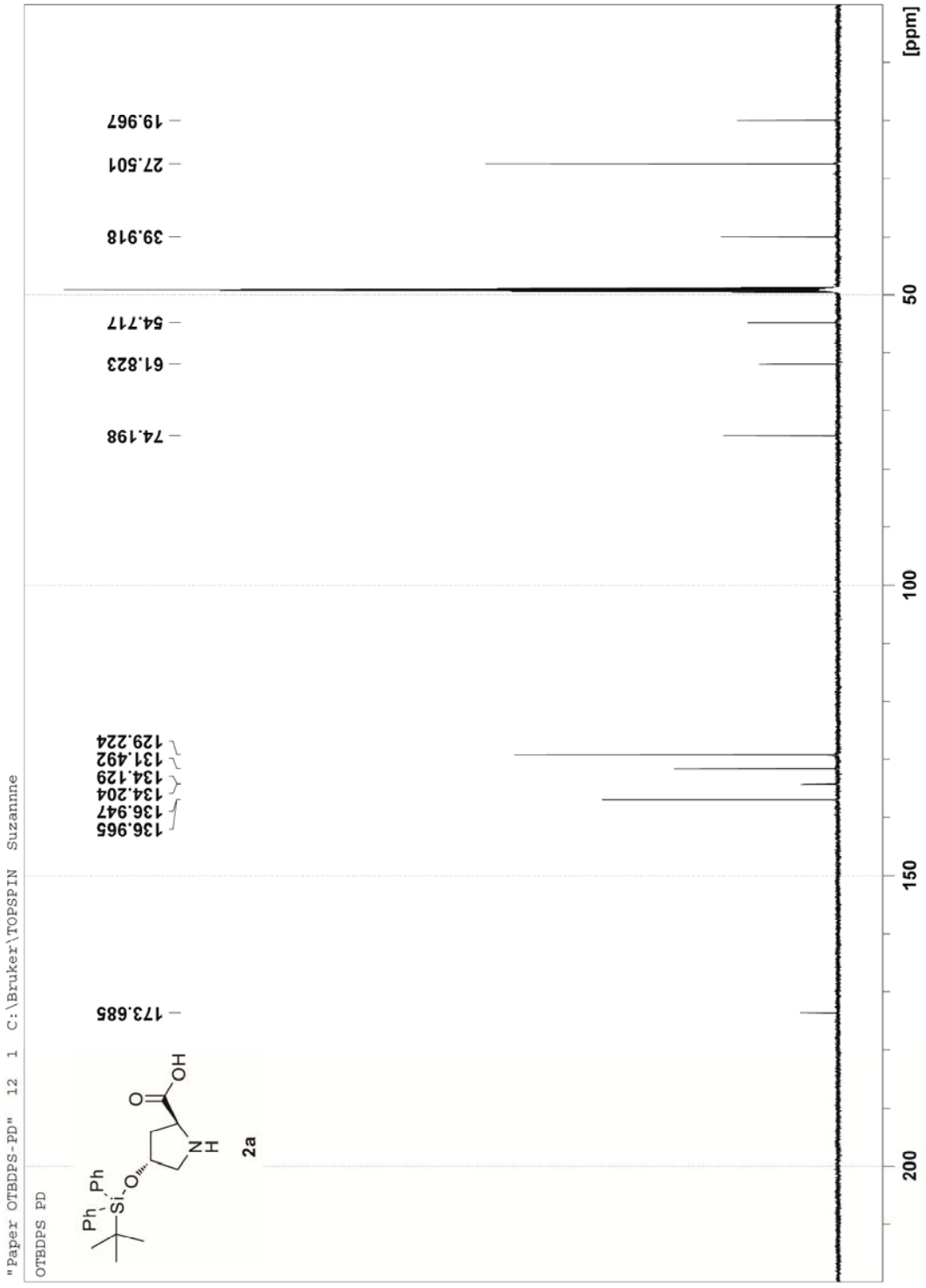
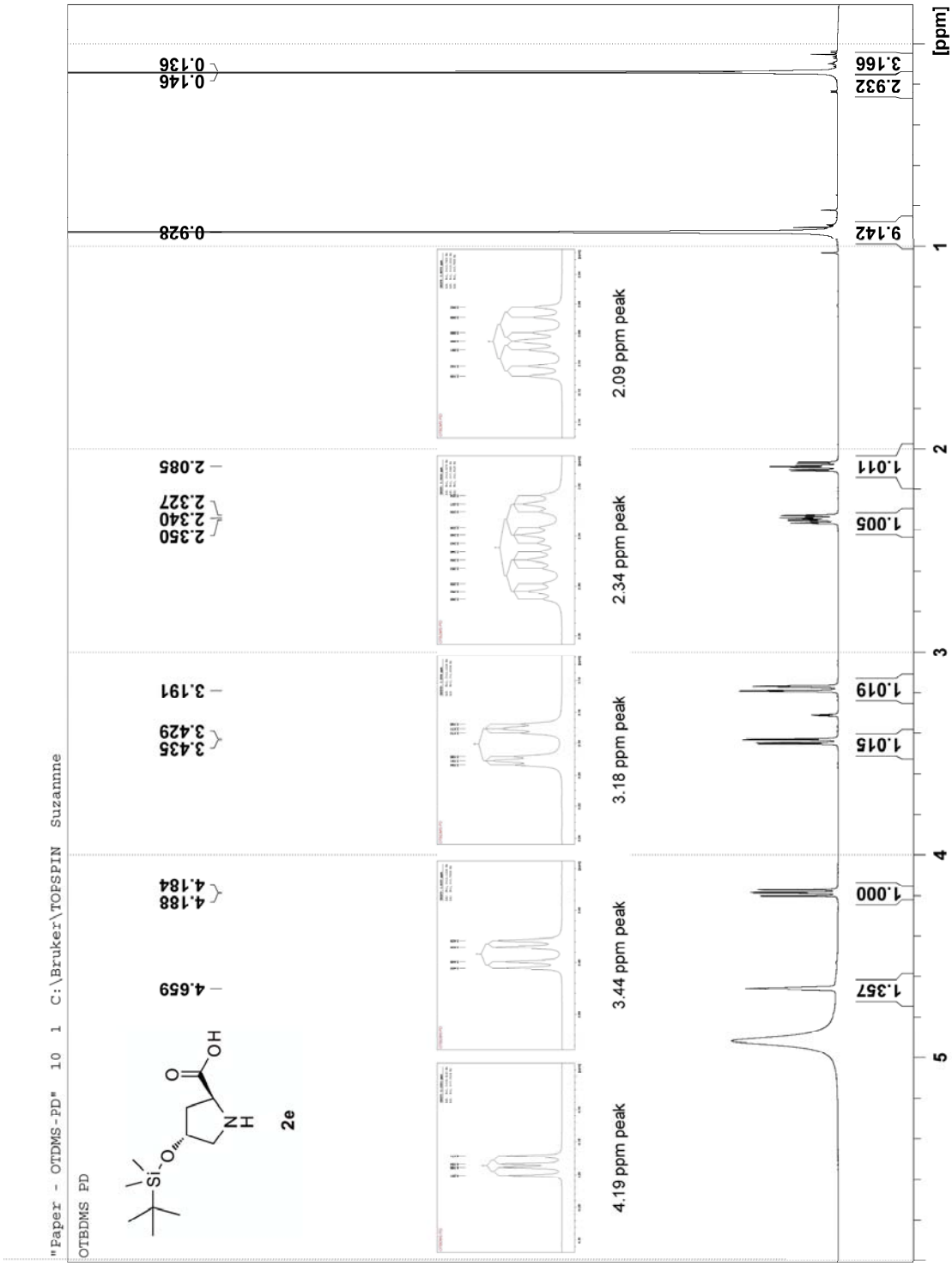
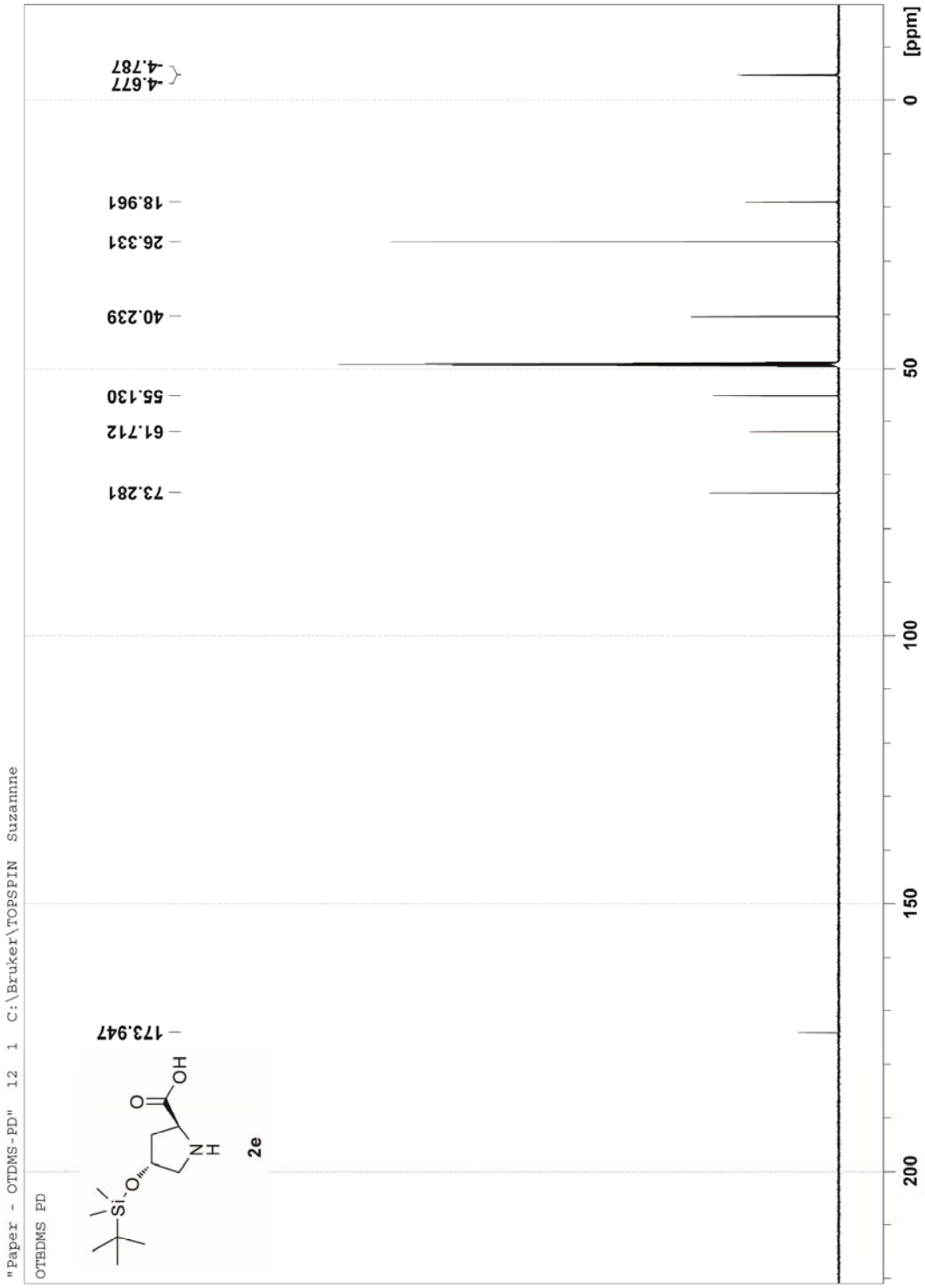
8.028
7.496
3.248
3.236
3.225
3.115
3.104
3.093
3.082
3.071
2.660
2.649
2.638
1.099
1.088
1g
12.000
1.989
2.011
2.040
0.966
1.928
[ppm]

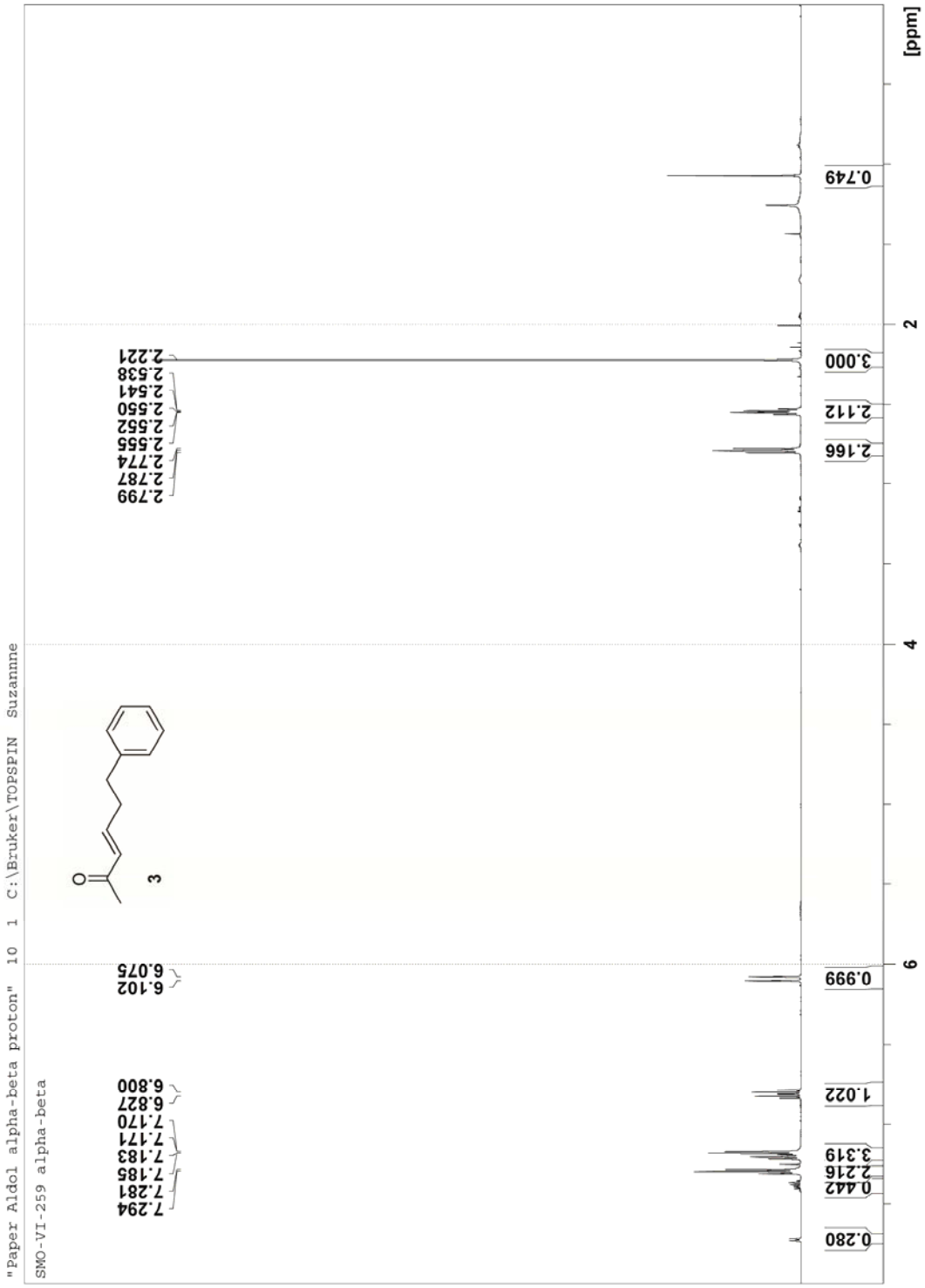

"Paper Urea 7 BAL-I-201 13C" 12 1 C:\Bruker\TCPSPIN Suzanne
BAL-I-201
157.505
143.583
133.506
133.288
133.069
132.850
127.565
125.765
123.965
122.164
118.934
115.406
115.381
115.356
50.026
45.699
41.242
20.916
1g
[ppm]
150
100
50

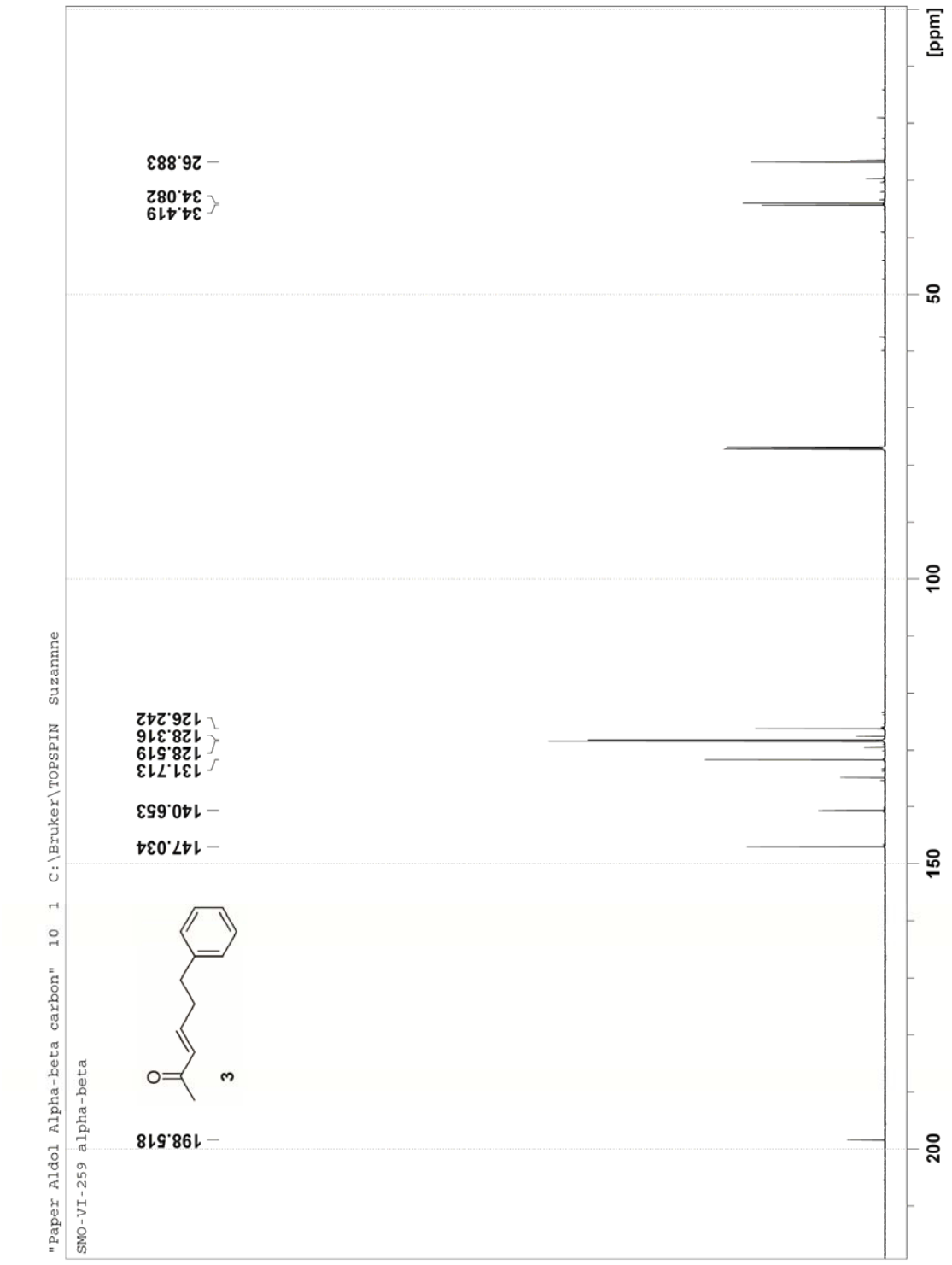

"Paper OTBDPS-PD" 10 1 C:\Bruker\TOPSPIN Suzannne
OTBDPS PD
Ph
Ph
Si
O
N
H
OH
O
2a
7.636
7.403
4.572
4.256
4.251
4.239
3.291
3.284
3.201
2.333
2.323
2.310
1.918
1.066
4.3 ppm peak
3.3 ppm peak
2.3 ppm peak
1.9 ppm peak
3.957
5.956
1.444
0.996
1.282
1.005
1.000
1.002
9.101
6
4
2
[ppm]

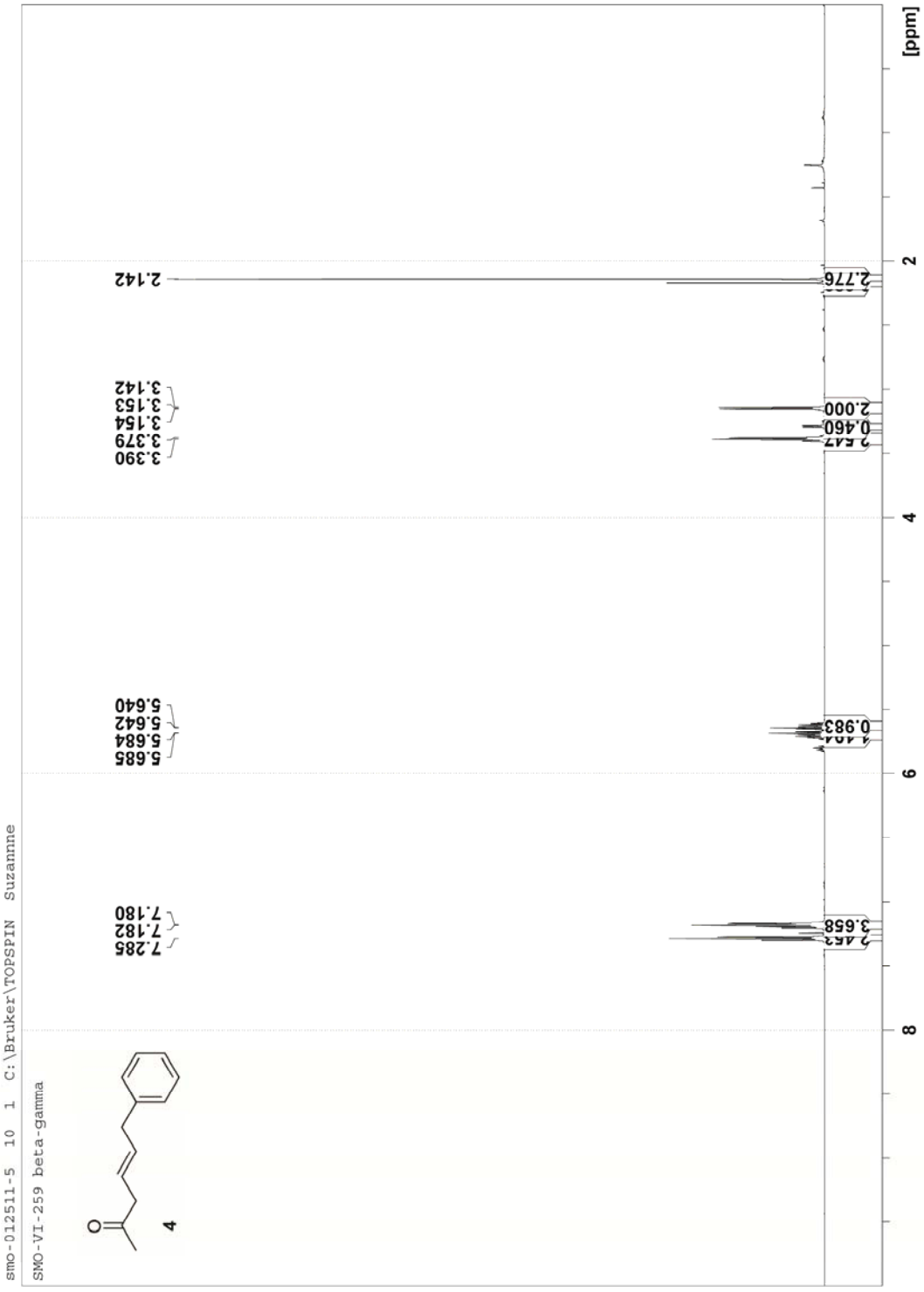

"Paper OTBDPS-PD" 12 1 C:\Bruker\TOPSPIN Suzannne
OTBDPS PD
173.685
136.965
136.947
134.204
134.129
131.492
129.224
74.198
61.823
54.717
39.918
27.501
19.967
2a
[ppm]
200
150
100
50

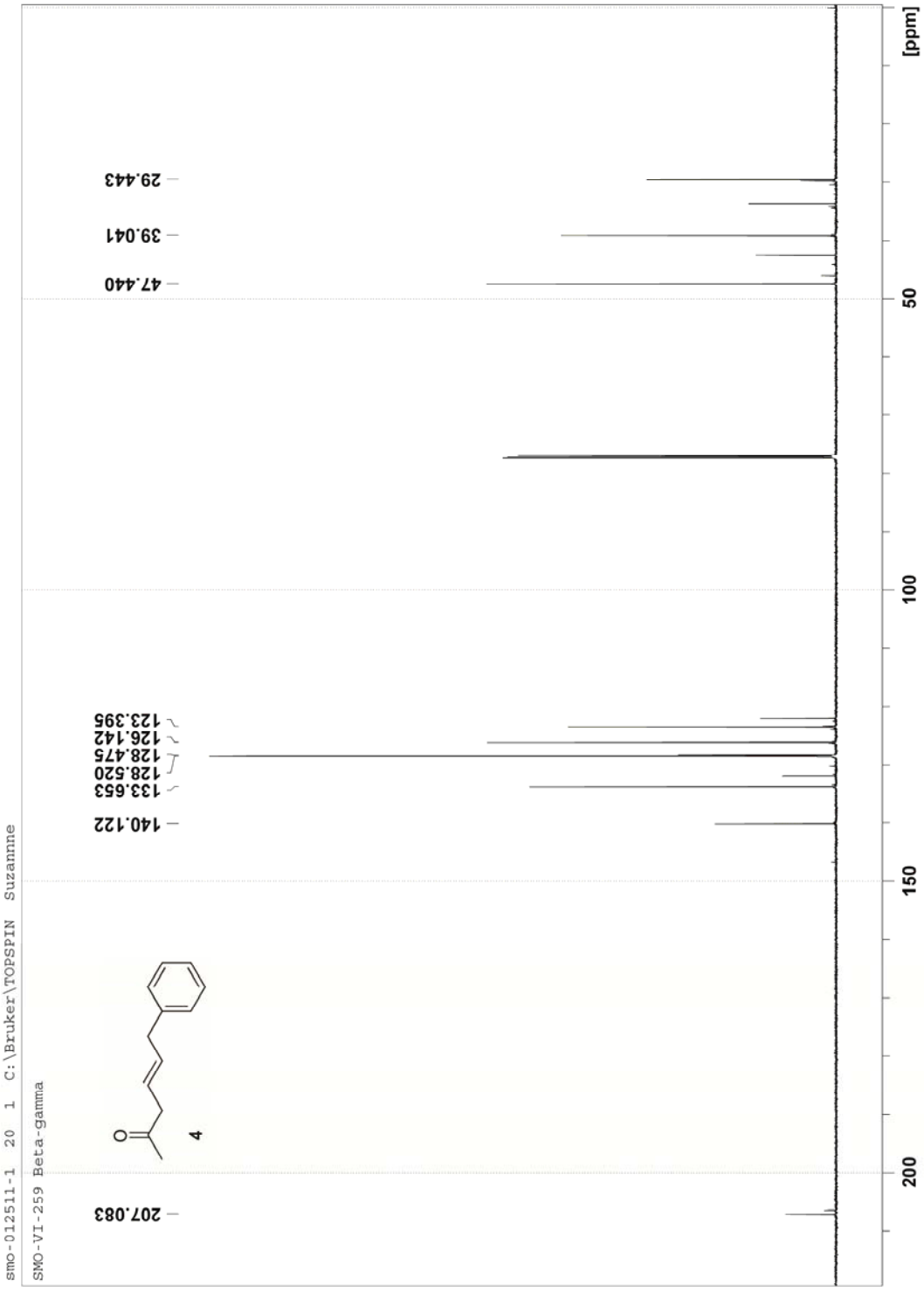

"Paper - OTDMS-PD" 10 1 C:\Bruker\TOPSPIN Suzannne
OTBDMS PD
2e
4.659
4.188
4.184
3.435
3.429
3.191
2.350
2.340
2.327
2.085
0.928
0.146
0.136
4.19 ppm peak
3.44 ppm peak
3.18 ppm peak
2.34 ppm peak
2.09 ppm peak
1.357
1.000
1.015
1.019
1.005
1.011
9.142
2.932
3.166
[ppm]

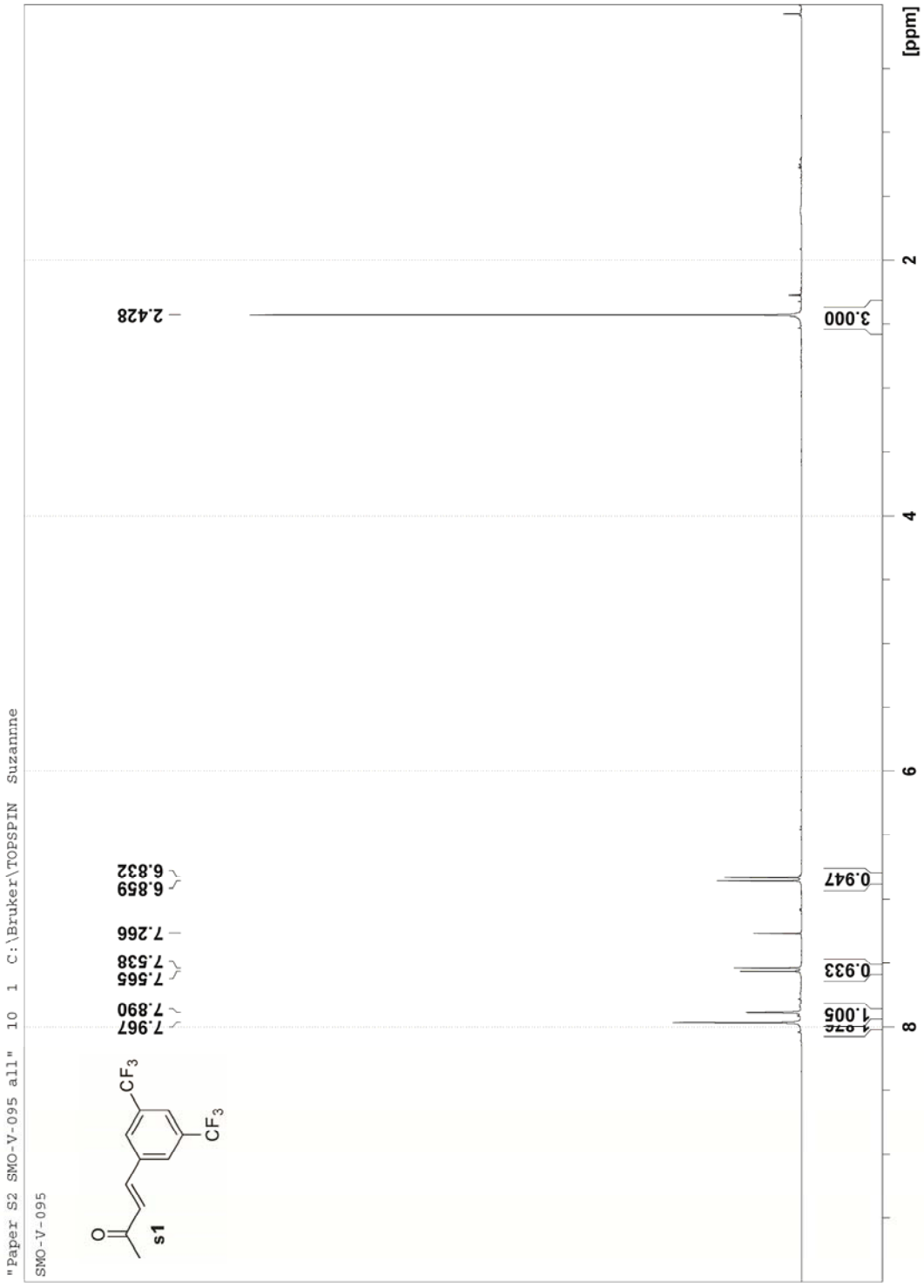

"Paper - OTDMS-PD" 12 1 C:\Bruker\TOPSPIN Suzannne
OTBDMS PD
2e
173.947
73.281
61.712
55.130
40.239
26.331
18.961
-4.677
-4.787
200
150
100
50
0
[ppm]


"Paper Aldol alpha-beta proton" 10 1 C:\Bruker\TOPSPIN Suzannne
SMO-VI-259 alpha-beta
3
7.294
7.281
7.185
7.183
7.171
7.170
6.827
6.800
6.102
6.075
2.799
2.787
2.774
2.555
2.552
2.550
2.541
2.538
2.221
0.280
0.442
2.216
3.319
1.022
0.999
6
2.166
2.112
3.000
4
0.749
2
[ppm]

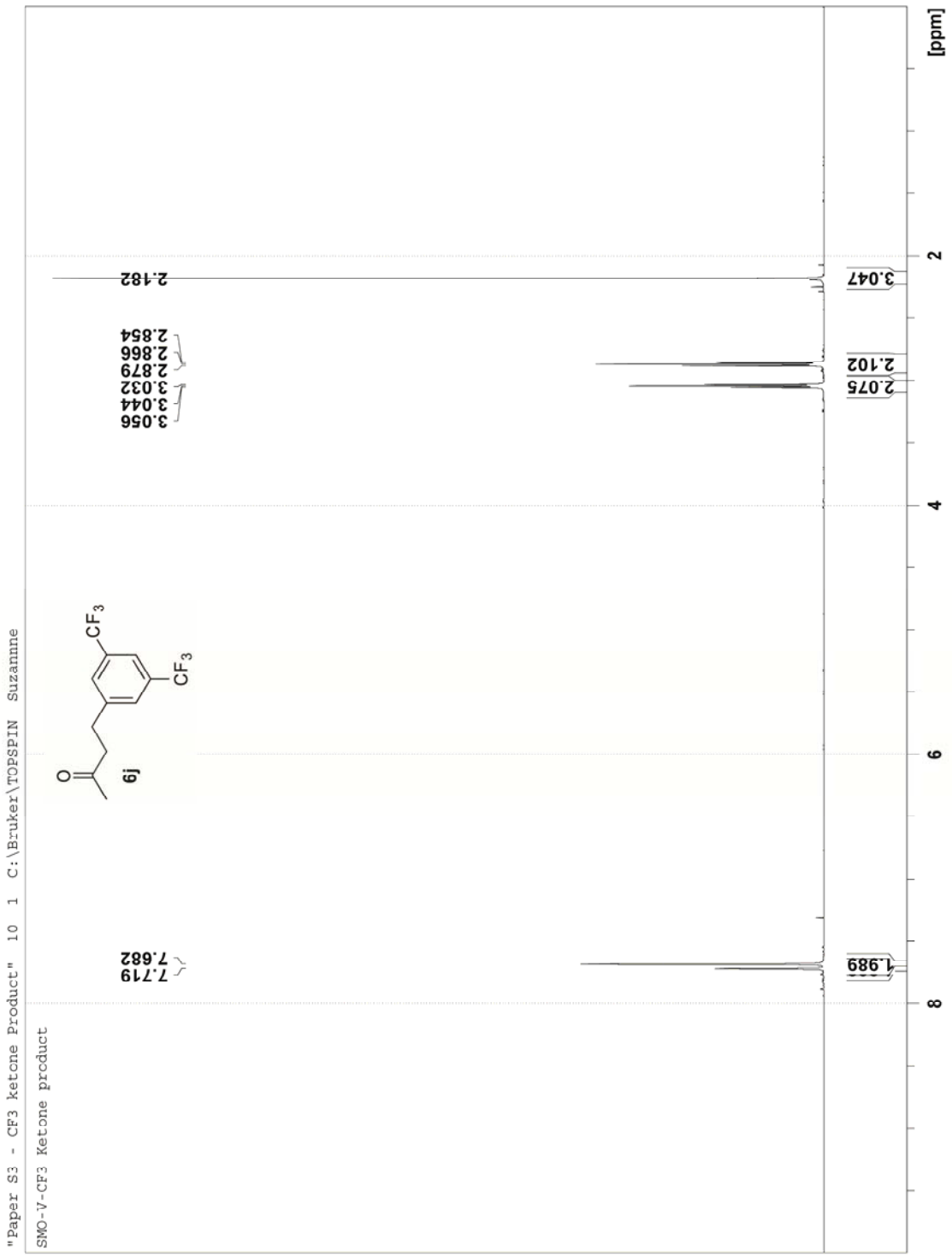

"Paper Aldol Alpha-beta carbon" 10 1 C:\Bruker\TOPSPIN Suzannne
SMO-VI-259 alpha-beta
198.518
147.034
140.653
131.713
128.519
128.316
126.242
34.419
34.082
26.883
3
200
150
100
50
[ppm]

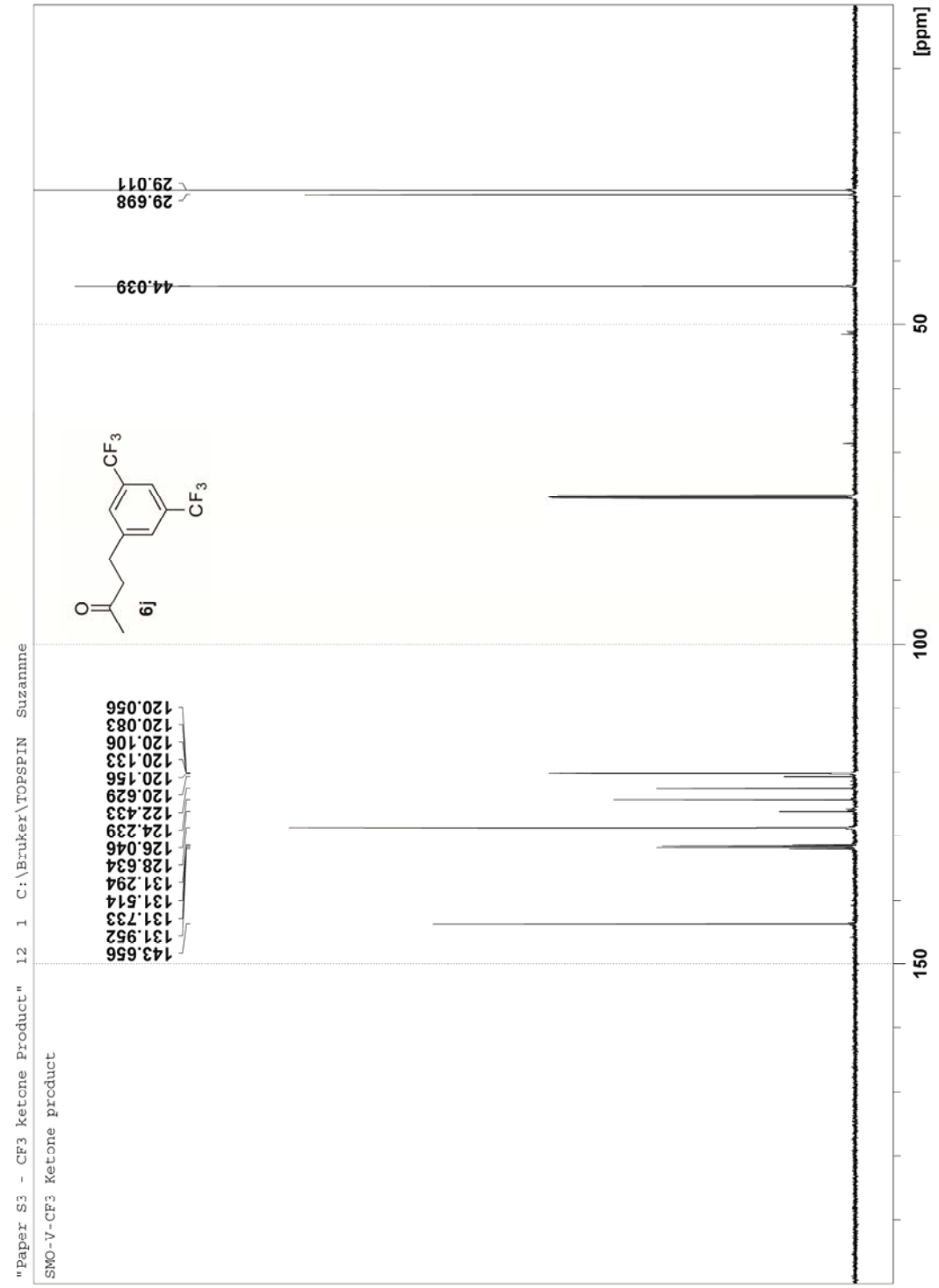

smo-012511-5 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-259 beta-gamma
4
7.285
7.182
7.180
5.685
5.684
5.642
5.640
3.390
3.379
3.154
3.153
3.142
2.142
2.776
3.658
0.983
2.000
0.460
[ppm]

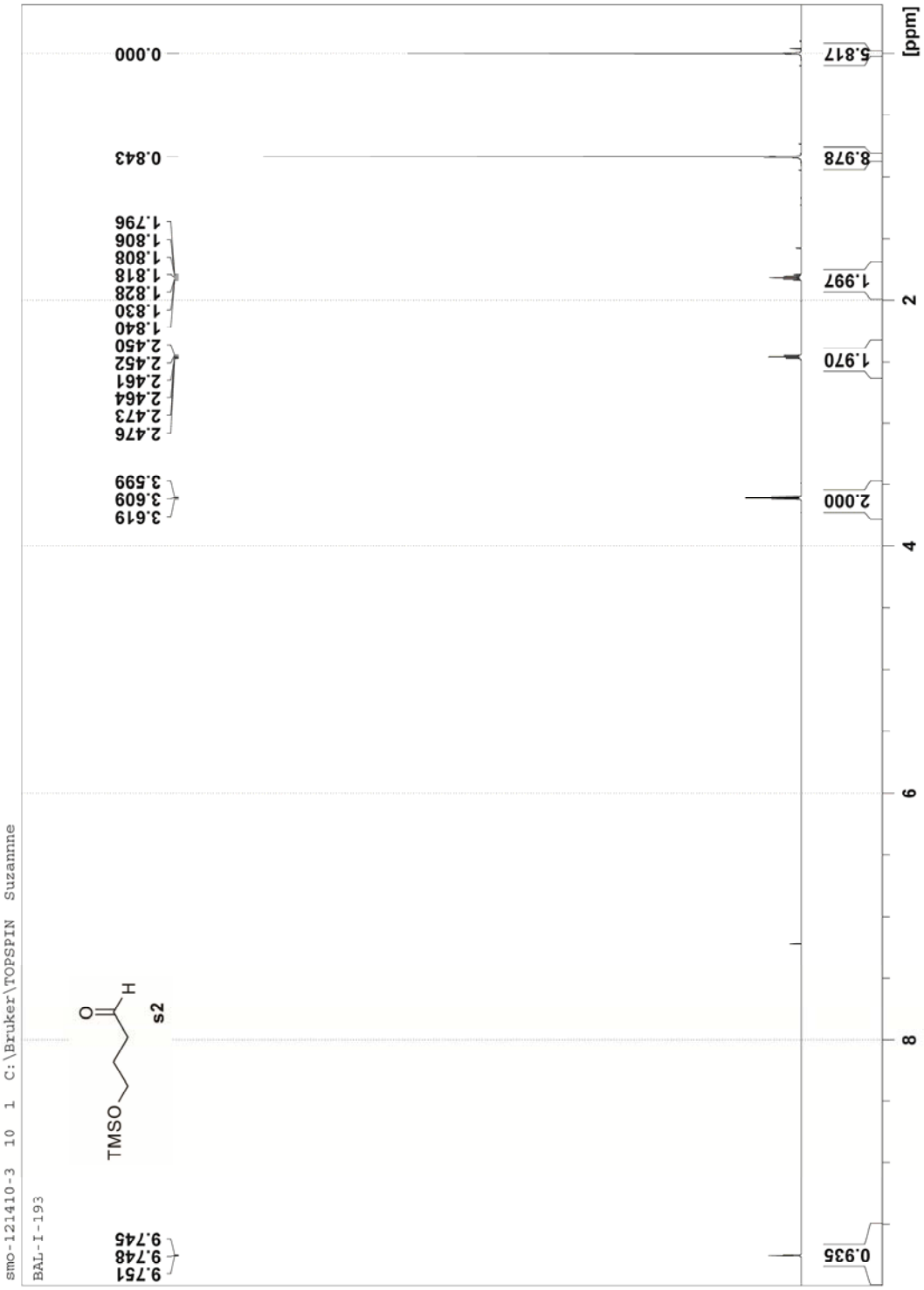

smo-012511-1 20 1 C:\Bruker\TOPSPIN Suzannne
SMO-VI-259 Beta-gamma
4
207.083
140.122
133.653
128.520
128.475
126.142
123.395
47.440
39.041
29.443
200
150
100
50
[ppm]

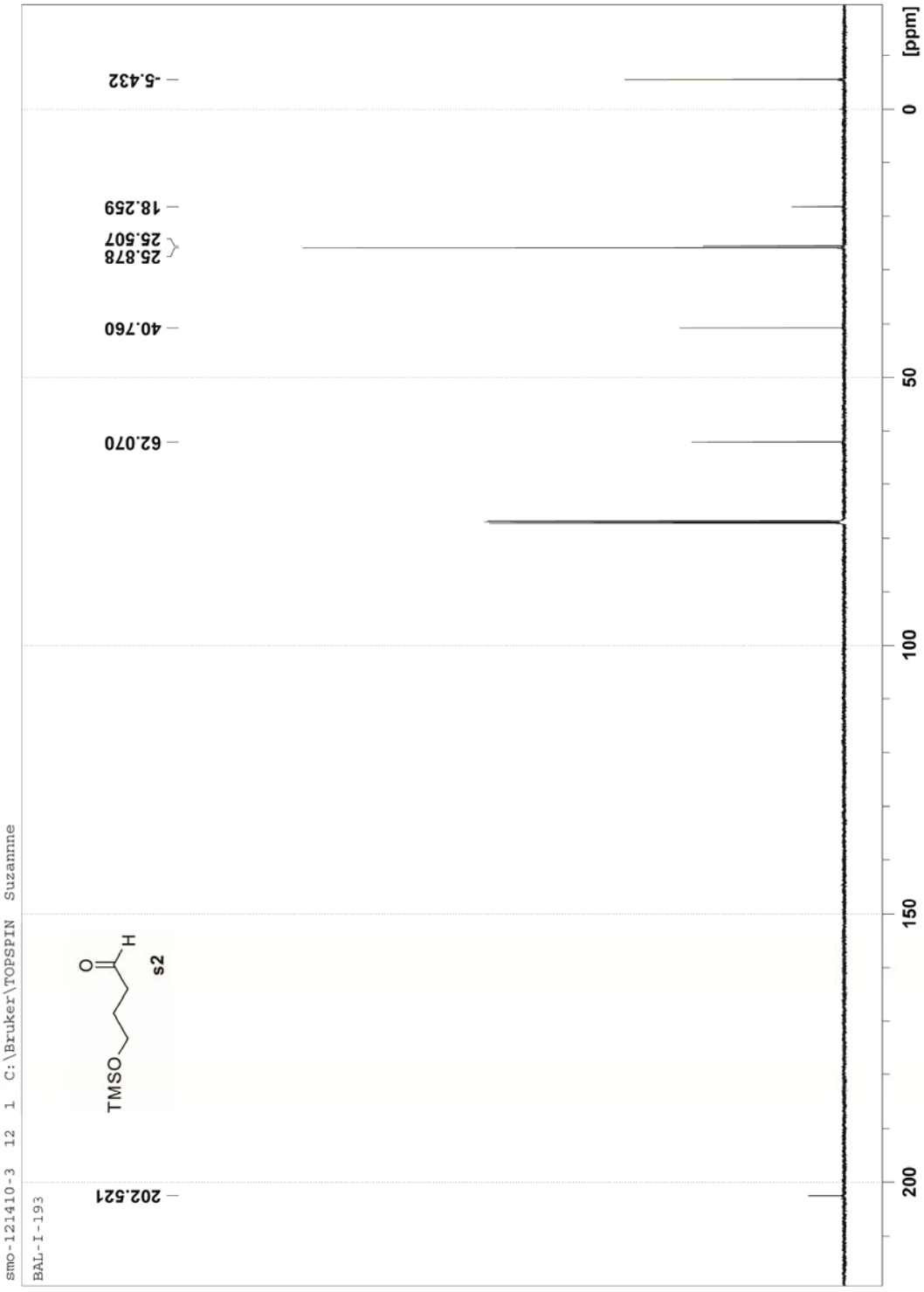

"Paper S2 SMO-V-095 all" 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-V-095
s1
O
CF3
CF3
7.967
7.890
7.565
7.538
7.266
6.859
6.832
2.428
1.005
0.933
0.947
3.000
8
6
4
2
[ppm]

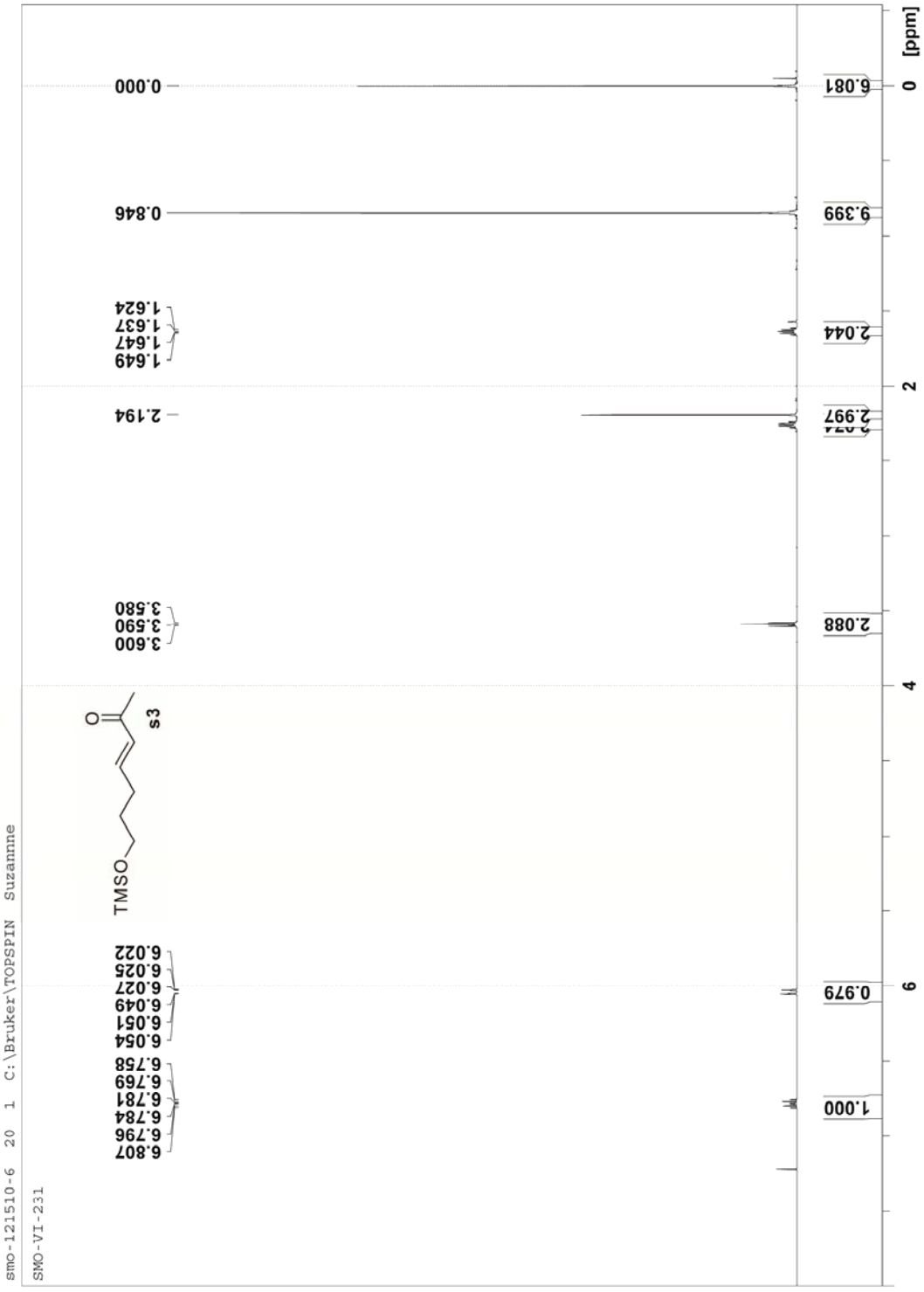
"Paper S2 SMO-V-095 all" 21 1 C:\Bruker\TOPSPIN Suzanne
SMO-V-095
197.071
139.247
136.697
132.914
132.691
132.467
132.245
130.000
127.783
125.690
123.881
123.520
123.496
123.474
122.073
120.263
28.114
s1
O
CF3
CF3
150
100
50
[ppm]

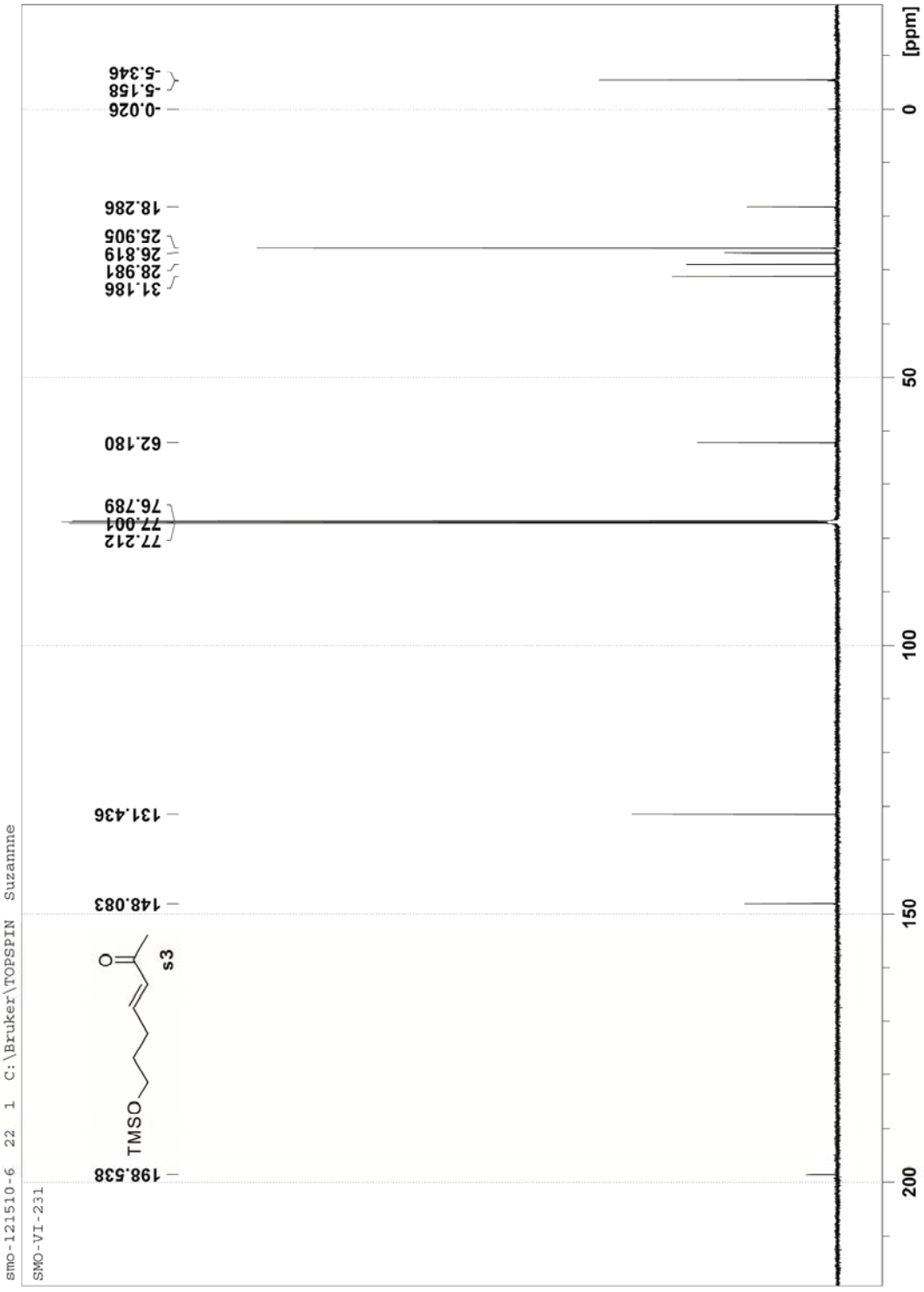

"Paper S3 - CF3 ketone Product" 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-V-CF3 Ketone product
7.719
7.682
3.056
3.044
3.032
2.879
2.866
2.854
2.182
1.989
2.075
2.102
3.047
6j
[ppm]

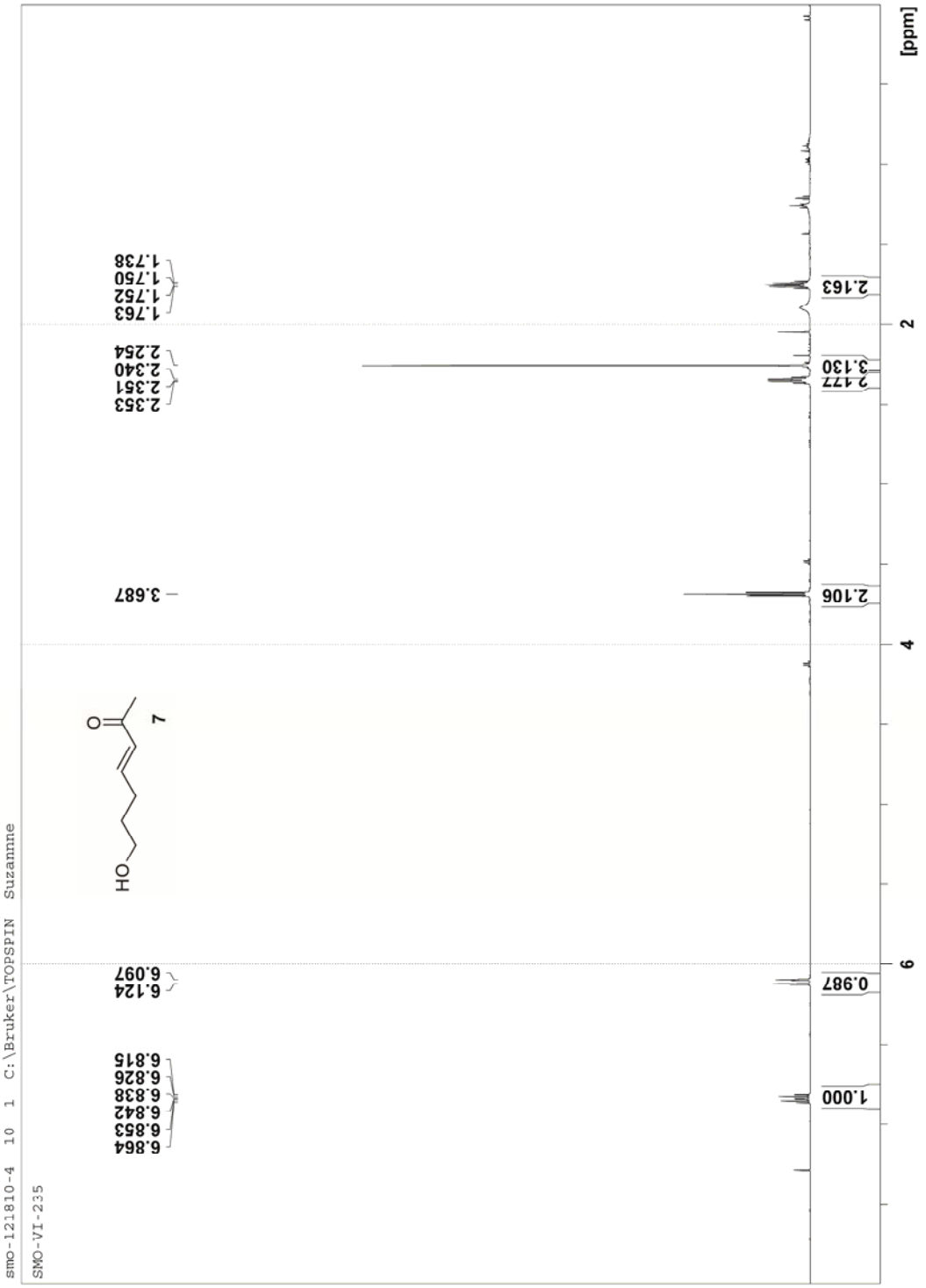

"Paper S3 - CF3 ketone Product" 12 1 C:\Bruker\TOPSPIN Suzanne
SMO-V-CF3 Ketone product
143.656
131.952
131.733
131.614
131.294
128.634
126.046
124.239
122.433
120.629
120.156
120.133
120.106
120.083
120.056
6j
44.039
29.698
29.011
[ppm]
150
100
50

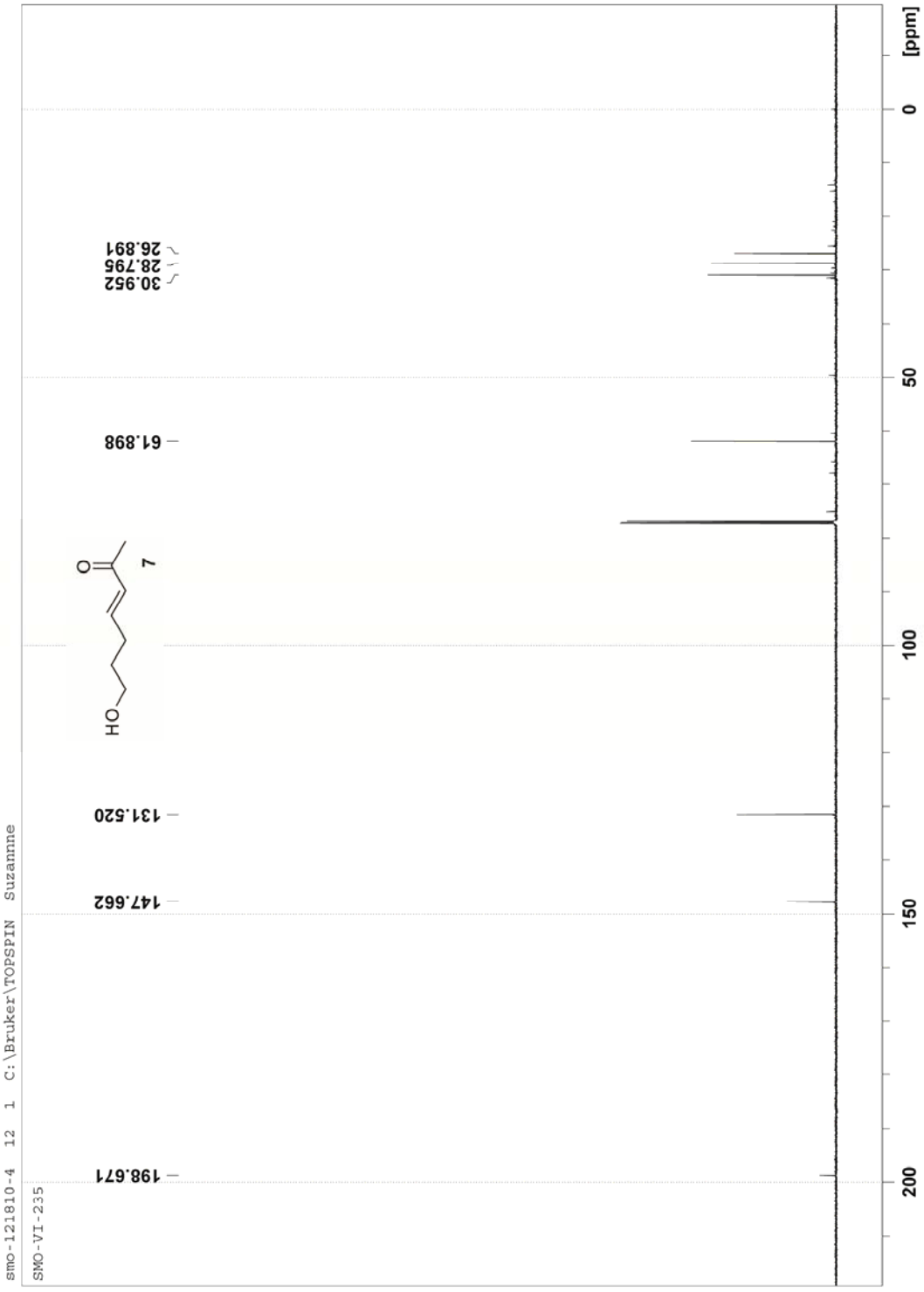

smo-121410-3 10 1 C:\Bruker\TOPSPIN Suzanne
BAL-I-193
TMSO
s2
H
O
9.751
9.748
9.745
3.619
3.609
3.599
2.476
2.473
2.464
2.461
2.452
2.450
1.840
1.830
1.828
1.818
1.808
1.806
1.796
0.843
0.000
0.935
2.000
1.970
1.997
8.978
5.817
[ppm]
8
6
4
2

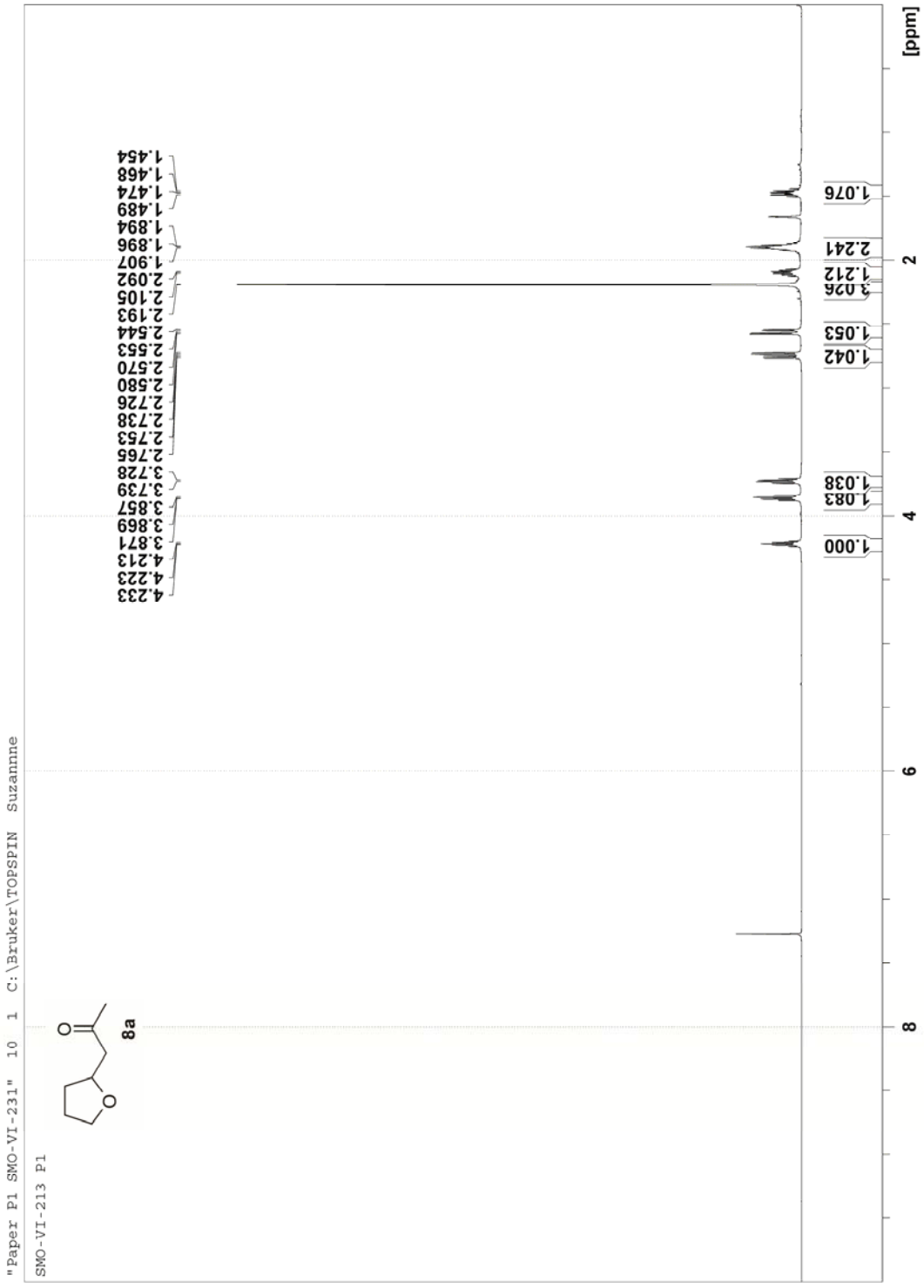

smo-121410-3 12 1 C:\Bruker\TOPSPIN Suzanne
BAL-I-193
TMSO
O
H
s2
202.521
62.070
40.760
25.878
25.507
18.259
-5.432
200
150
100
50
0
[ppm]

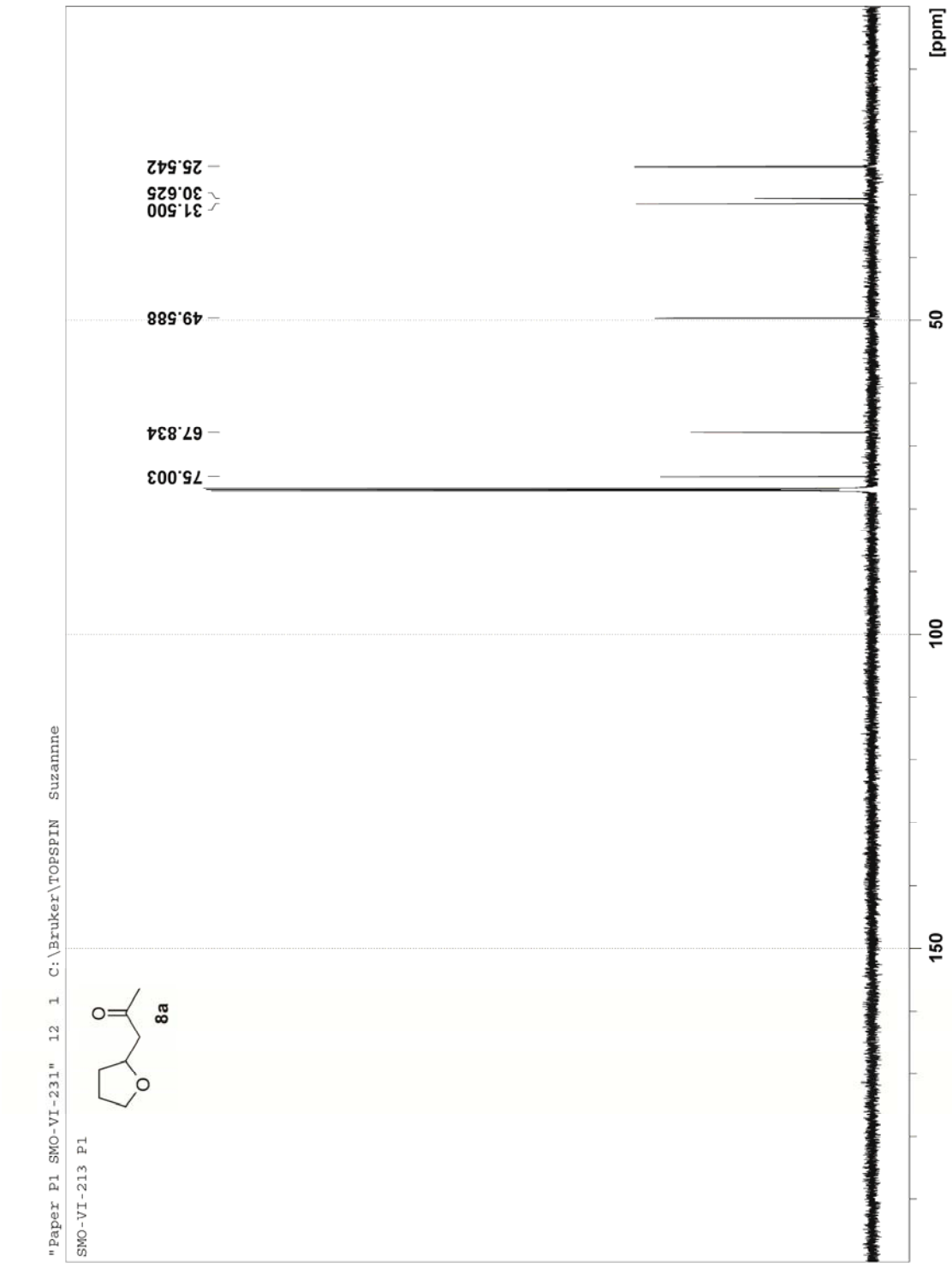

smo-121510-6 20 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-231
TMSO
s3
6.807
6.796
6.784
6.781
6.769
6.758
6.054
6.051
6.049
6.027
6.025
6.022
3.600
3.590
3.580
2.194
1.649
1.647
1.637
1.624
0.846
0.000
6.081
9.399
2.044
2.997
2.088
0.979
1.000
[ppm]

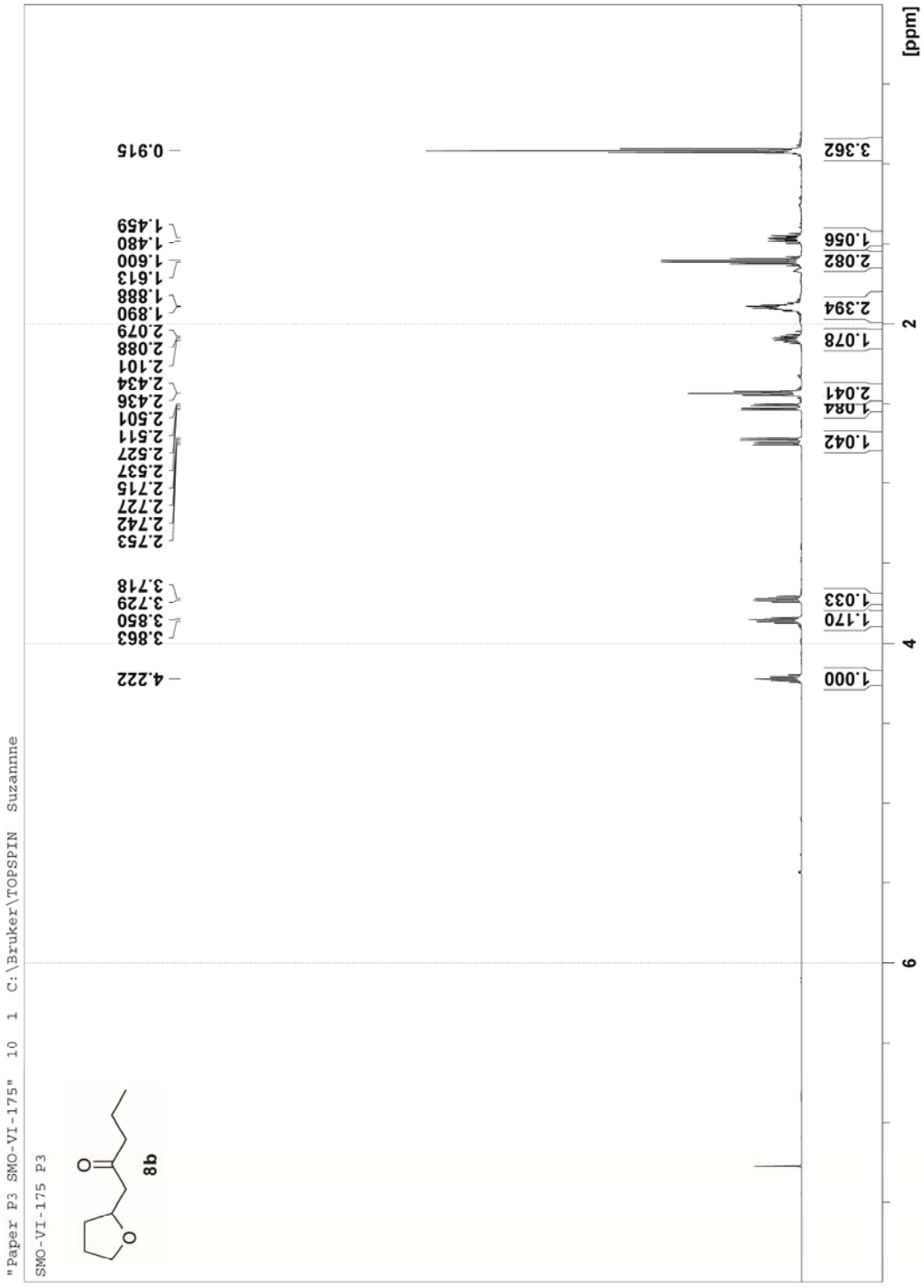

smo-121510-6 22 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-231
198.538
148.083
131.436
77.212
77.001
76.789
62.180
31.186
28.981
26.819
25.905
18.286
-0.026
-5.158
-5.346
TMSO
O
s3
[ppm]
0
50
100
150
200

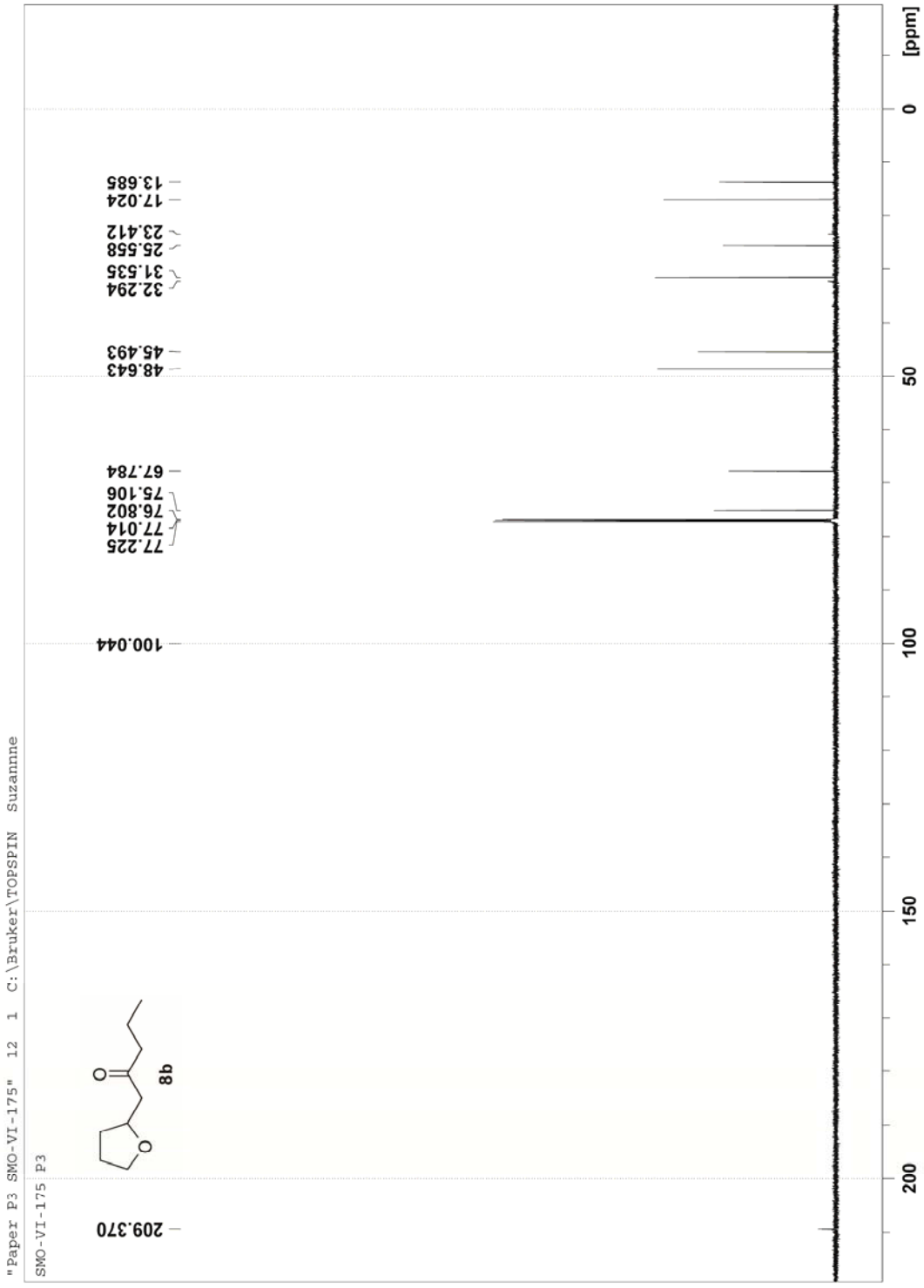

smo-121810-4 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-235
6.864
6.853
6.842
6.838
6.826
6.815
6.124
6.097
3.687
2.353
2.351
2.340
2.254
1.763
1.752
1.750
1.738
1.000
0.987
2.106
2.177
3.130
2.163
HO
7
6
4
2
[ppm]

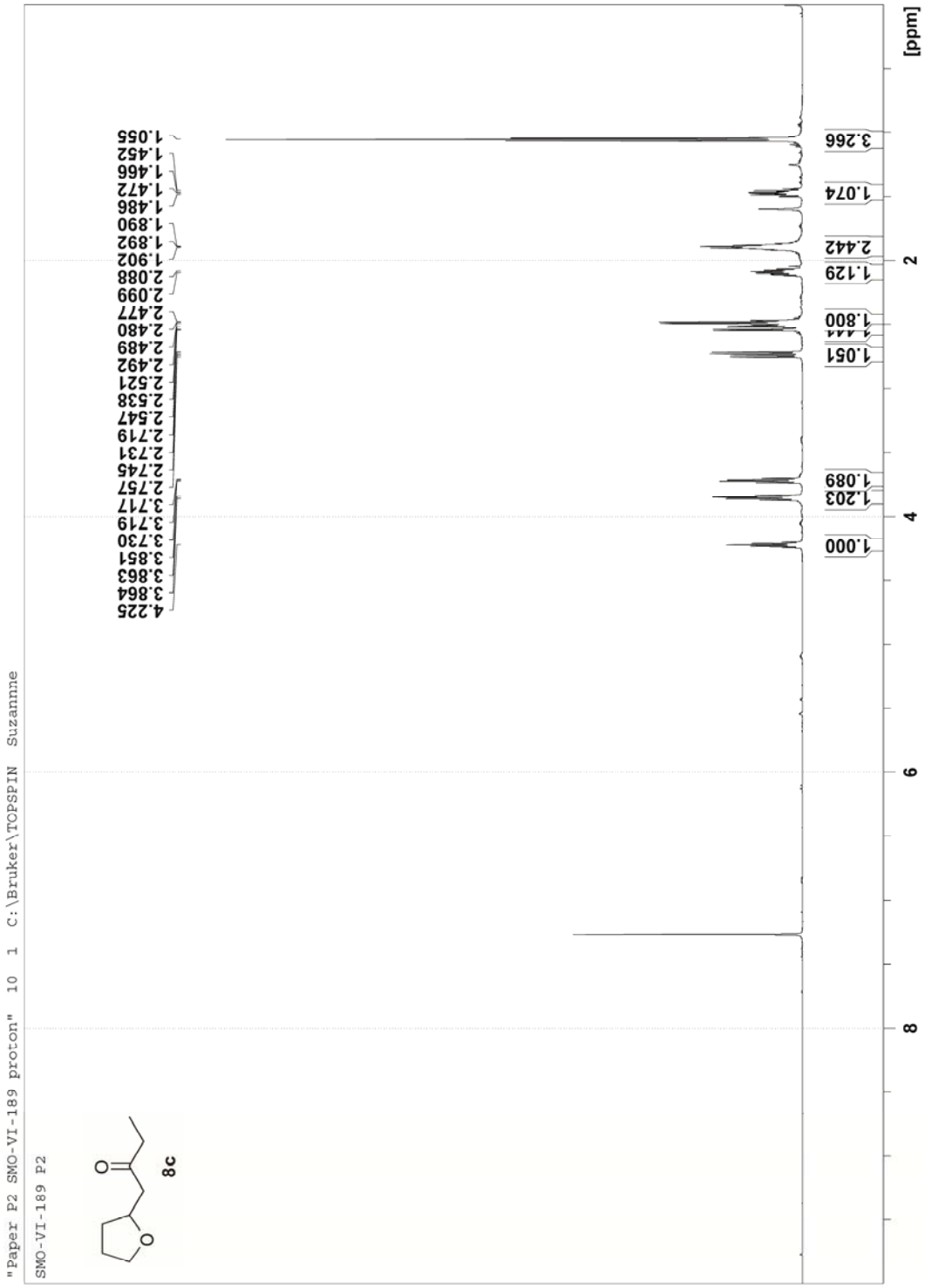

smo-121810-4 12 1 C:\Bruker\TOPSPIN Suzannne
SMO-VI-235
198.671
147.662
131.520
61.898
30.952
28.795
26.891
HO
O
7
0
50
100
150
200
[ppm]


"Paper P1 SMO-VI-231" 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-213 P1
8a
4.233
4.223
4.213
3.871
3.869
3.857
3.739
3.728
2.765
2.753
2.738
2.726
2.580
2.570
2.553
2.544
2.193
2.105
2.092
1.907
1.896
1.894
1.489
1.474
1.468
1.454
1.076
2.241
1.212
3.026
1.053
1.042
1.038
1.083
1.000
8
6
4
2
[ppm]

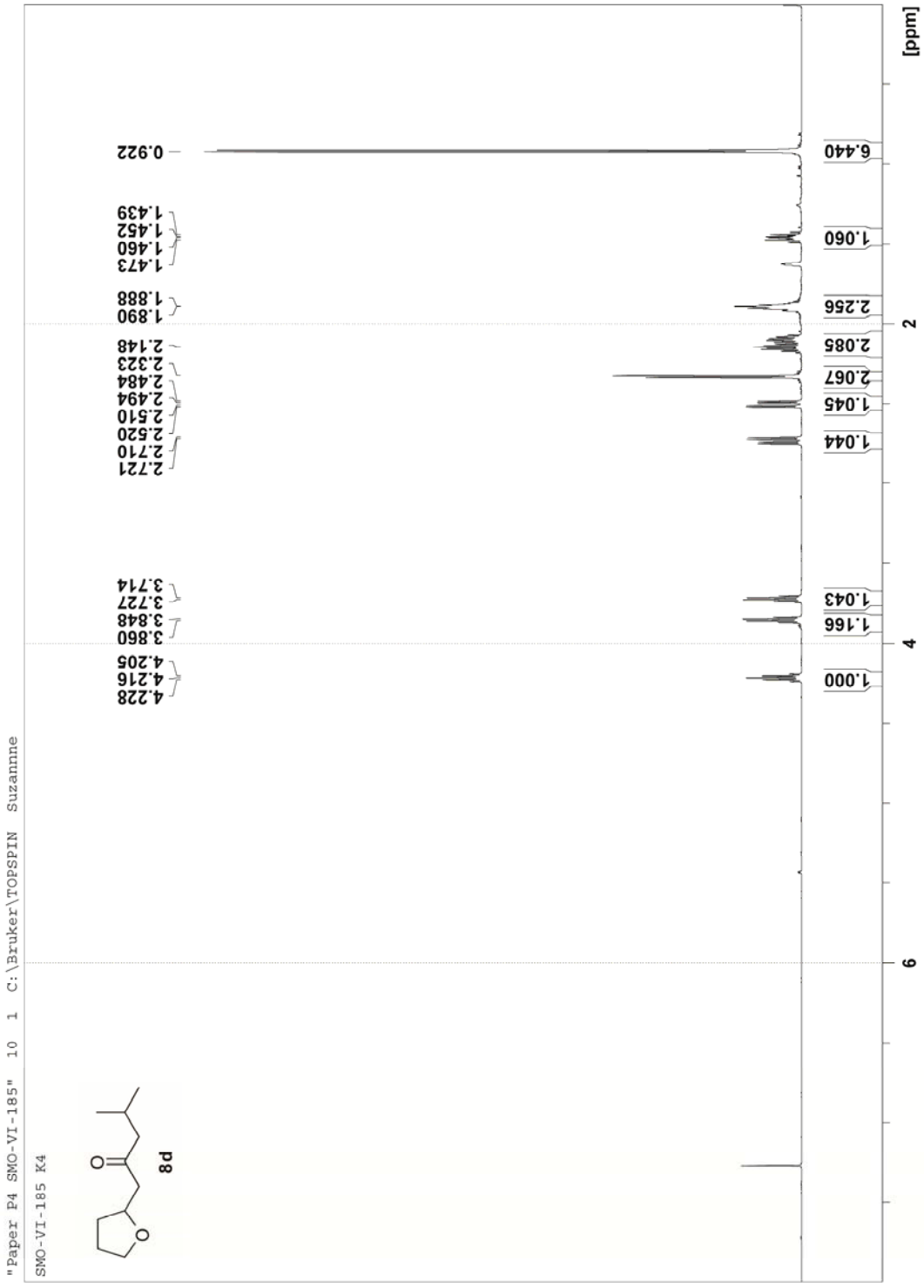

"Paper P1 SMO-VI-231" 12 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-213 P1
8a
O
O
25.542
30.625
31.500
49.588
67.834
75.003
150
100
50
[ppm]

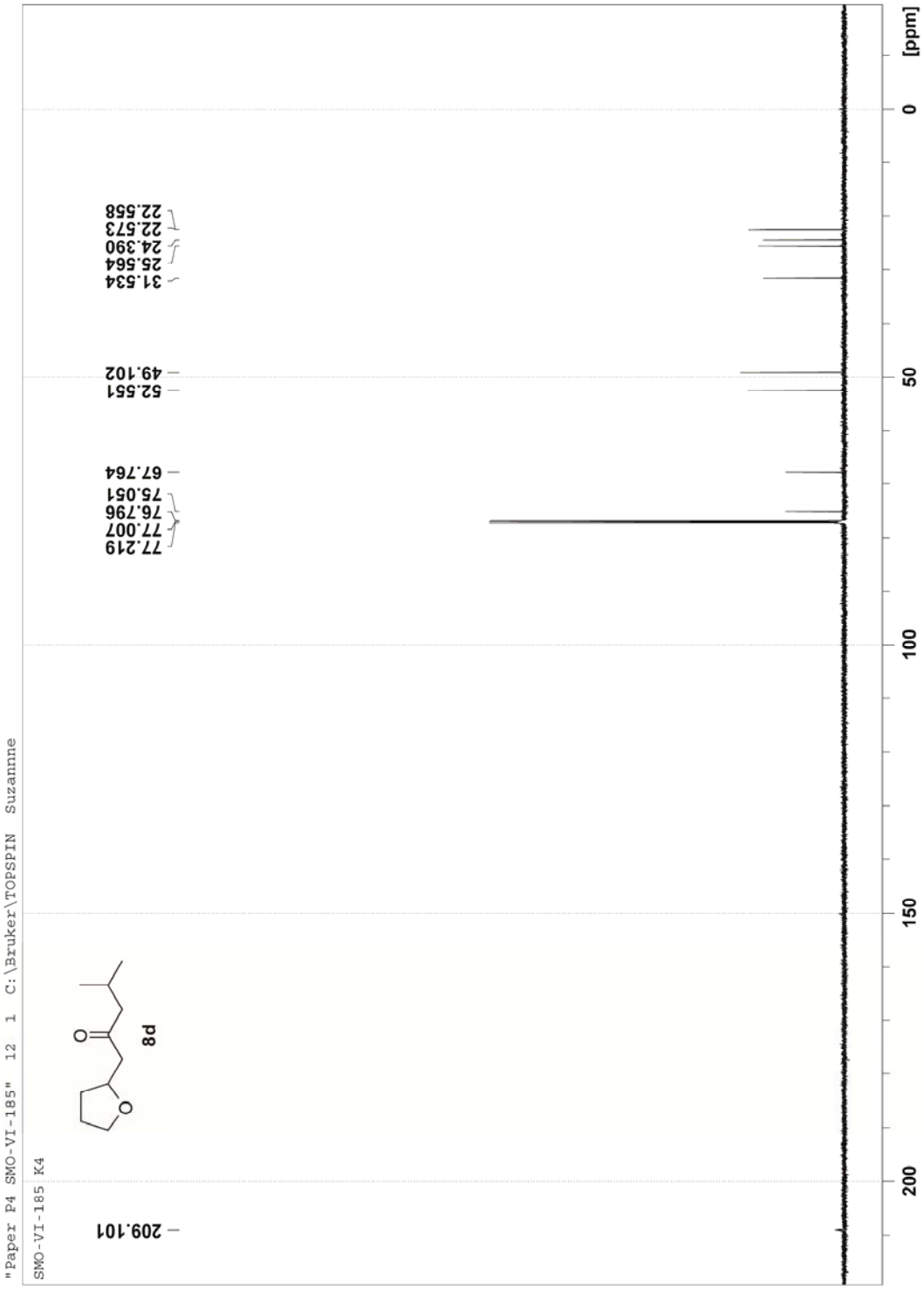

"Paper P3 SMO-VI-175" 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-175 P3
8b
0.915
1.459
1.480
1.600
1.613
1.888
1.890
2.079
2.088
2.101
2.434
2.436
2.501
2.511
2.527
2.537
2.715
2.727
2.742
2.753
3.718
3.729
3.850
3.863
4.222
3.362
1.056
2.082
2.394
1.078
2.041
1.084
1.042
1.033
1.170
1.000
6
4
2
[ppm]

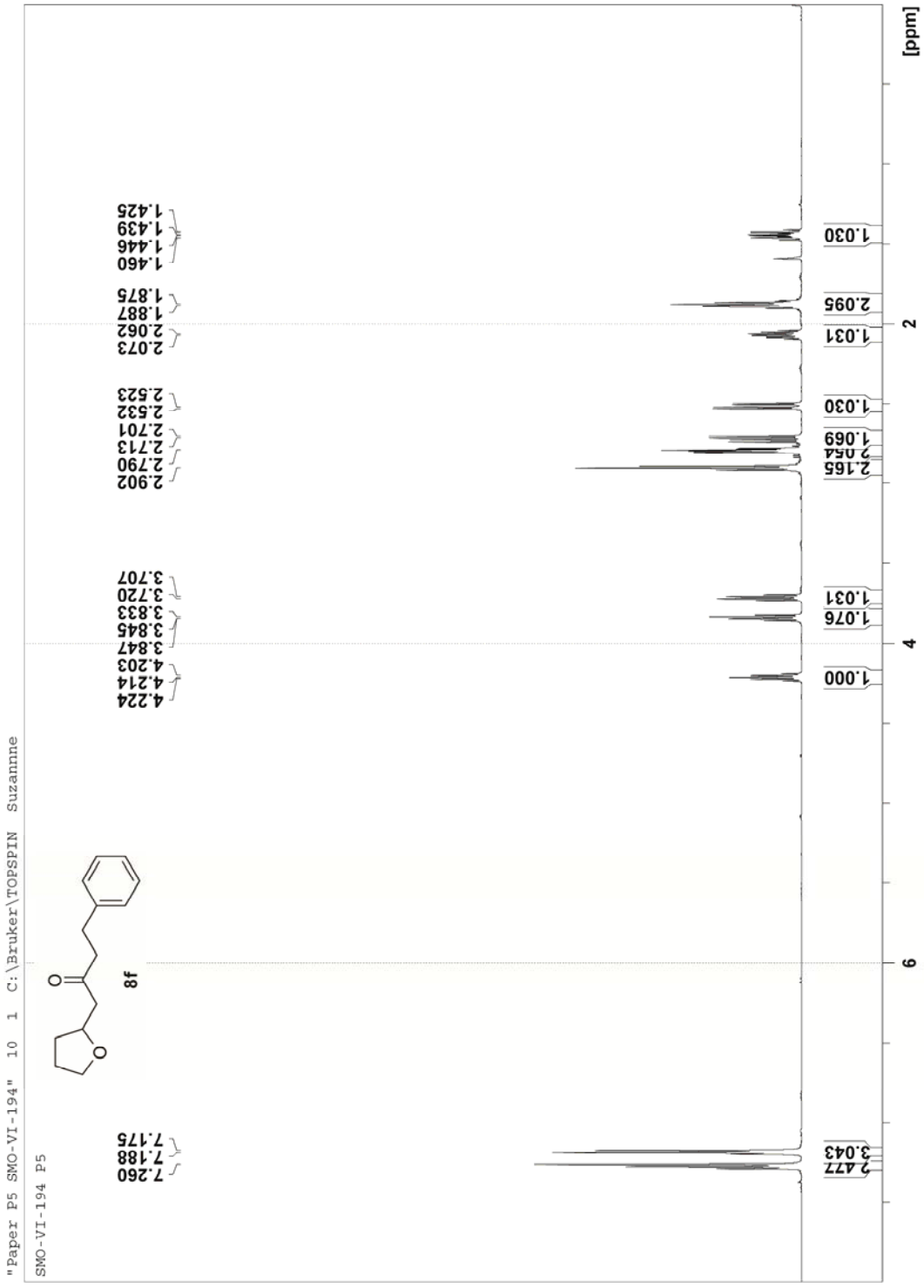

"Paper P3 SMO-VI-175" 12 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-175 P3
8b
209.370
100.044
77.225
77.014
76.802
75.106
67.784
48.643
45.493
32.294
31.535
25.558
23.412
17.024
13.685
200
150
100
50
0
[ppm]


"Paper P2 SMO-VI-189 proton" 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-189 P2
8c
4.225
3.864
3.863
3.851
3.730
3.719
3.717
2.757
2.745
2.731
2.719
2.547
2.538
2.521
2.492
2.489
2.480
2.477
2.099
2.088
1.902
1.892
1.890
1.486
1.472
1.466
1.452
1.055
3.266
1.074
2.442
1.129
1.800
1.444
1.051
1.089
1.203
1.000
8
6
4
2
[ppm]

"Paper P2 SMO-VI-189 proton" 12 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-189 P2
8c
7.567
25.558
31.542
36.712
48.321
67.804
75.171
150
100
50
[ppm]


"Paper P4 SMO-VI-185" 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-185 K4
8d
0.922
1.439
1.452
1.460
1.473
1.888
1.890
2.148
2.323
2.484
2.494
2.510
2.520
2.710
2.721
3.714
3.727
3.848
3.860
4.205
4.216
4.228
6.440
1.060
2.256
2.085
2.067
1.045
1.044
1.043
1.166
1.000
[ppm]


"Paper P4 SMO-VI-185" 12 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-185 K4
8d
209.101
77.219
77.007
76.796
75.051
67.764
52.551
49.102
31.534
25.564
24.390
22.573
22.558
200
150
100
50
0
[ppm]


"Paper P5 SMO-VI-194" 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-194 P5
8f
7.260
7.188
7.175
4.224
4.214
4.203
3.847
3.845
3.833
3.720
3.707
2.902
2.790
2.713
2.701
2.532
2.523
2.073
2.062
1.887
1.875
1.460
1.446
1.439
1.425
2.477
3.043
1.000
1.076
1.031
2.054
1.069
2.165
1.030
1.031
2.095
1.030
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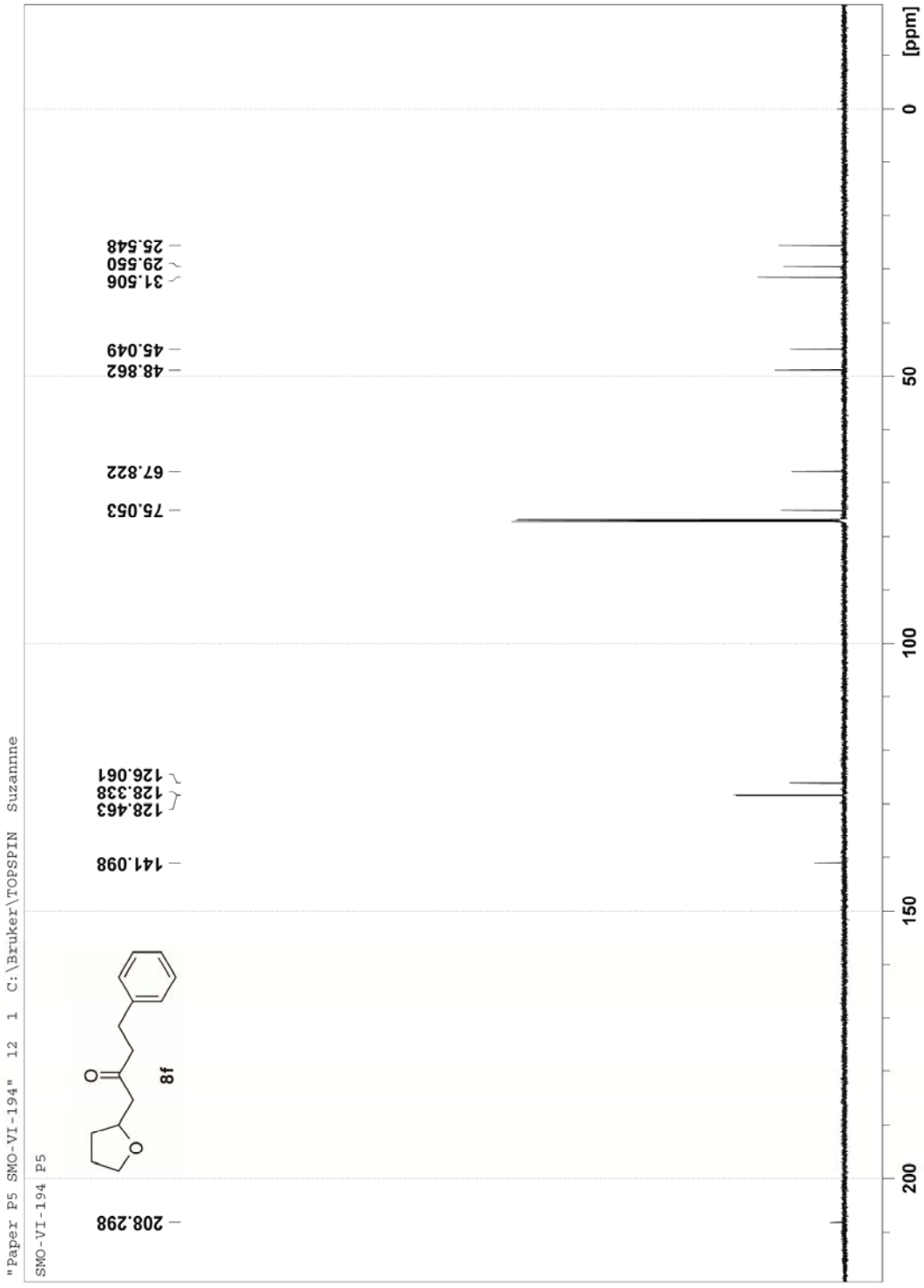
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SMO-VI-194 P5
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141.098
128.463
128.338
126.061
75.053
67.822
48.862
45.049
31.506
29.550
25.548
8f
0
50
100
150
200
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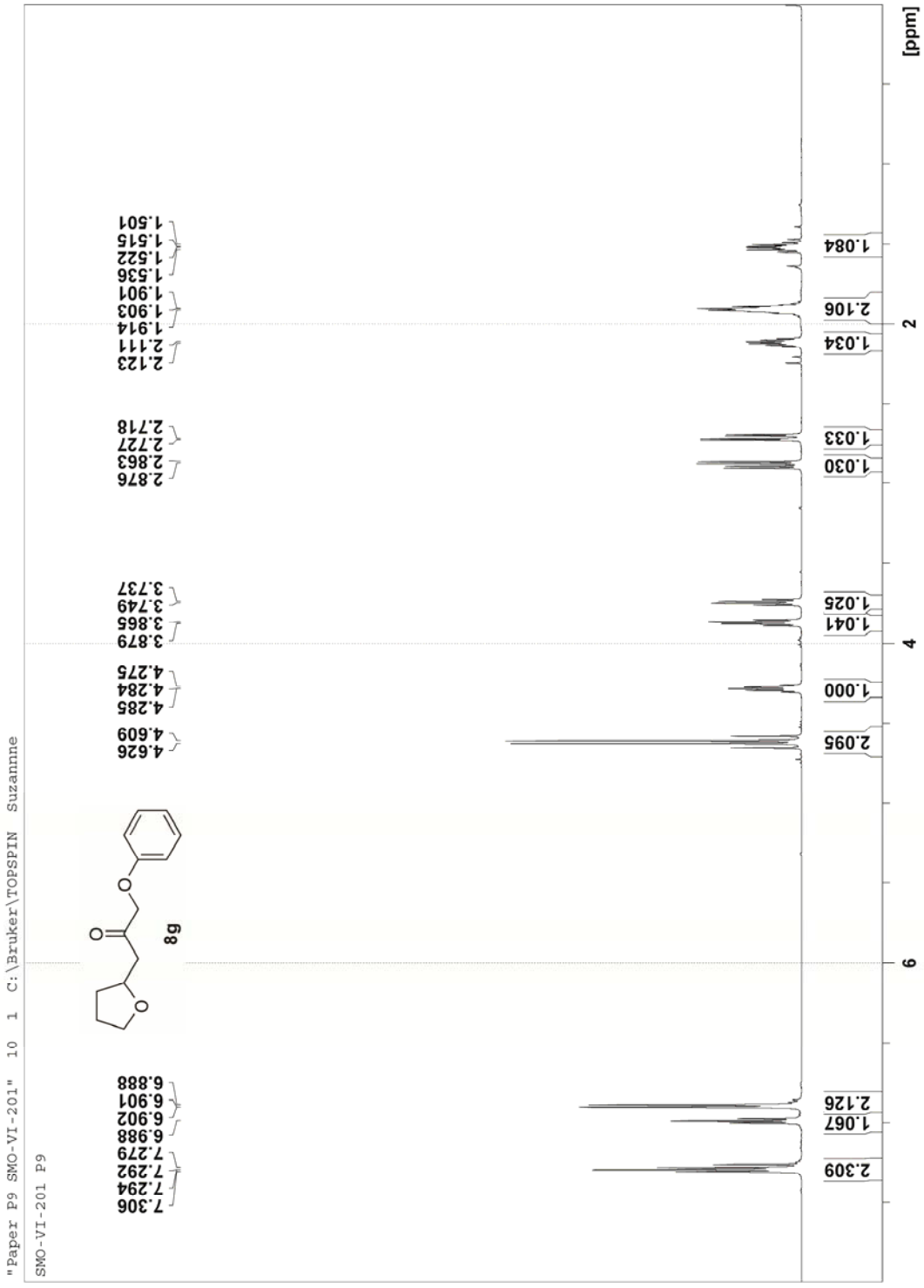
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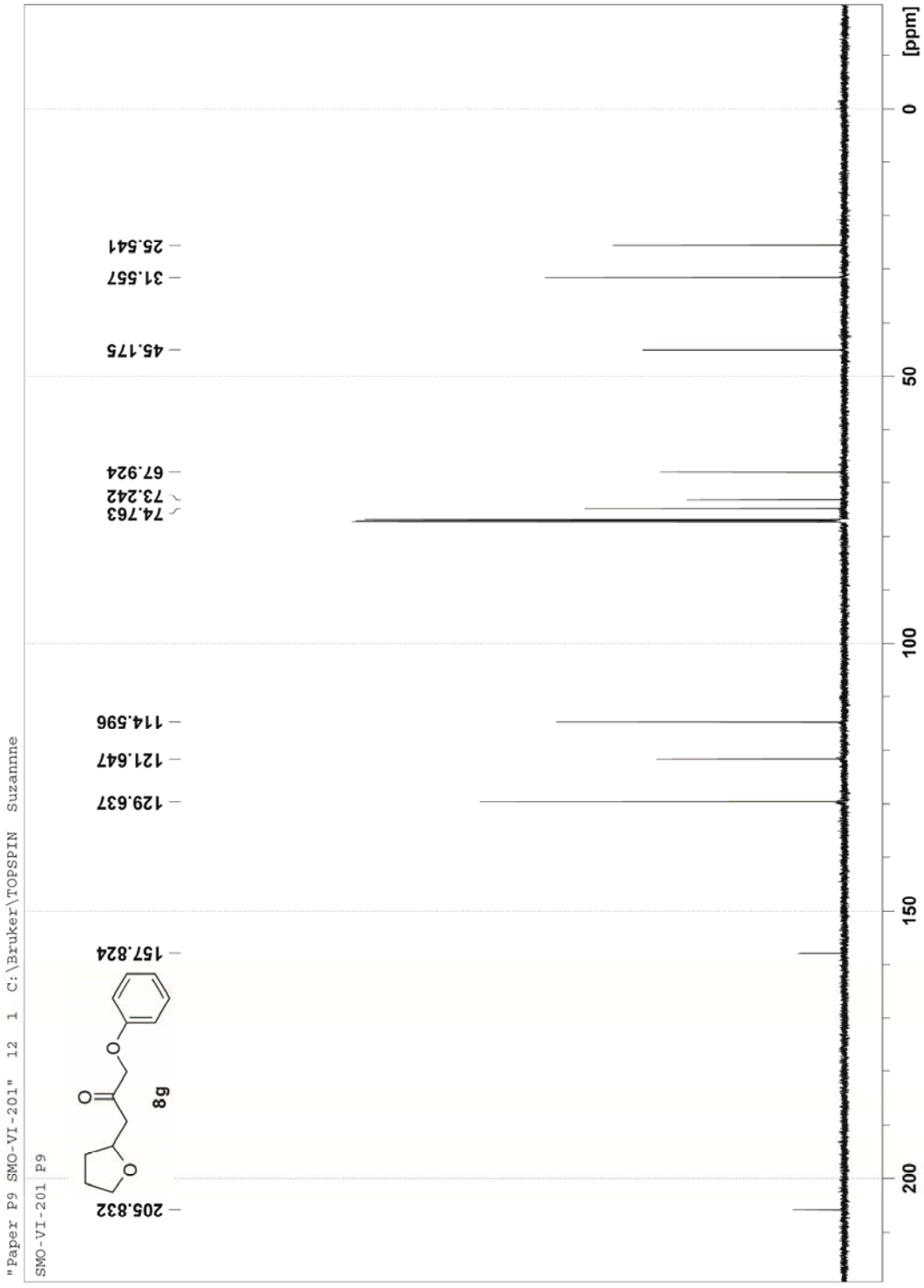
SMO-VI-201 P9
8g
7.306
7.294
7.292
7.279
6.988
6.902
6.901
6.888
4.626
4.609
4.285
4.284
4.275
3.879
3.865
3.749
3.737
2.876
2.863
2.727
2.718
2.123
2.111
1.914
1.903
1.901
1.536
1.522
1.515
1.501
2.309
1.067
2.126
2.095
1.000
1.041
1.025
1.030
1.033
1.034
2.106
1.084
6
4
2
[ppm]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SMO-VI-201 P9
205.832
157.824
129.637
121.647
114.596
74.763
73.242
67.924
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31.557
25.541
8g
0
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100
150
200
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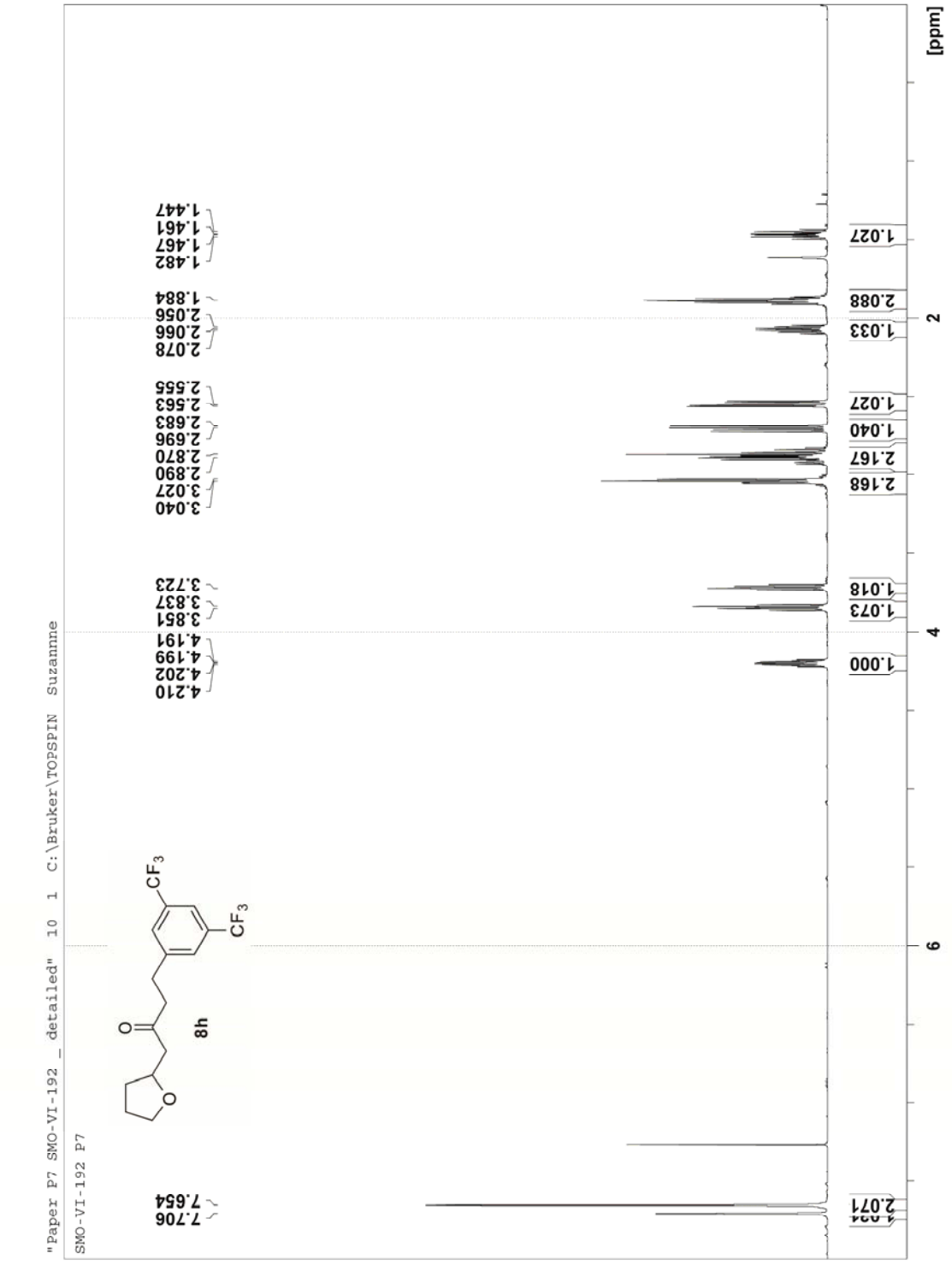
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SMO-VI-192 P7
8h
7.706
7.654
4.210
4.202
4.199
4.191
3.851
3.837
3.723
3.040
3.027
2.890
2.870
2.696
2.683
2.563
2.555
2.078
2.066
2.056
1.884
1.482
1.467
1.461
1.447
2.071
1.000
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1.018
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2.167
1.040
1.027
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1.027
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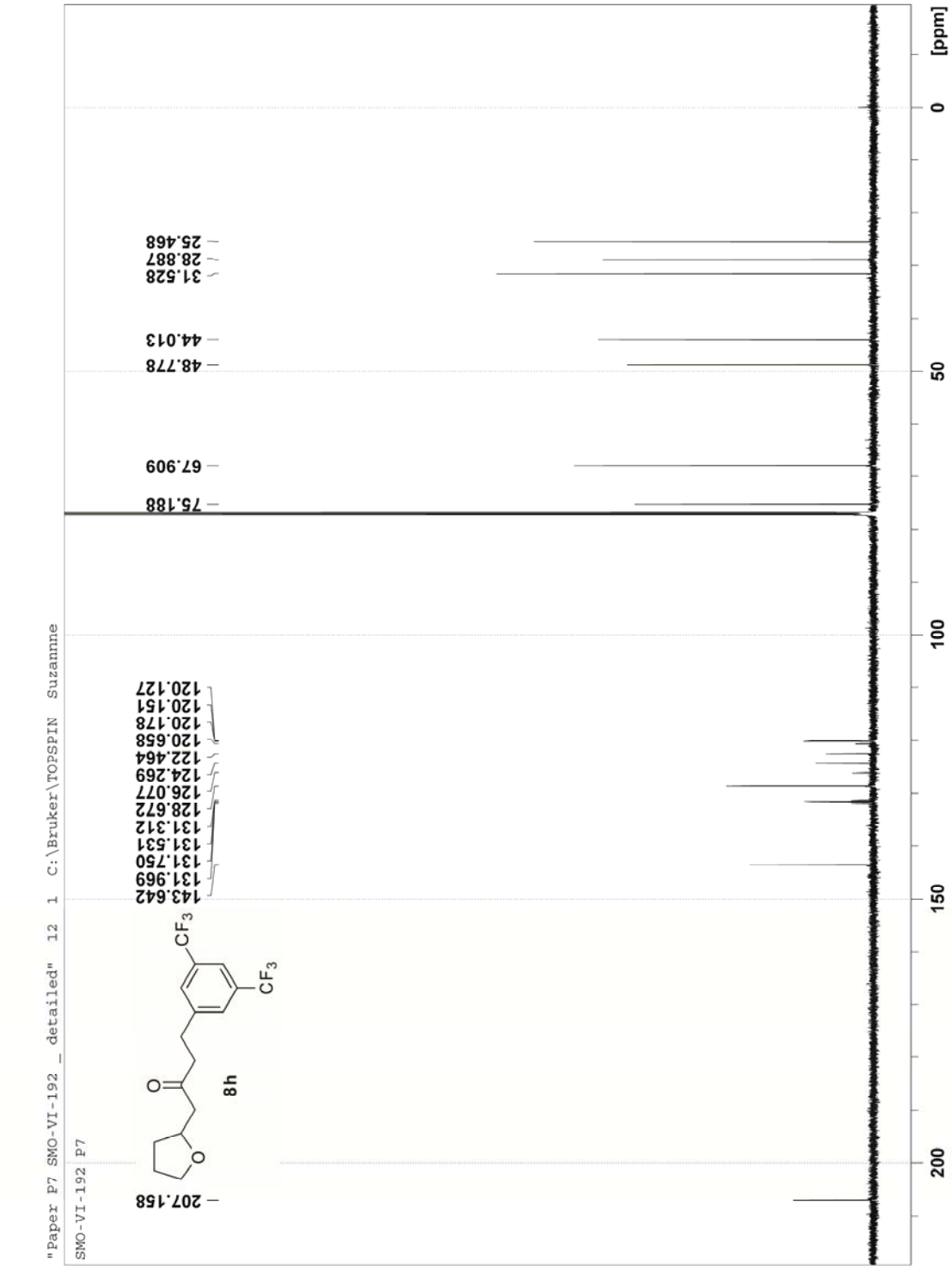
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SMO-VI-192 P7
207.158
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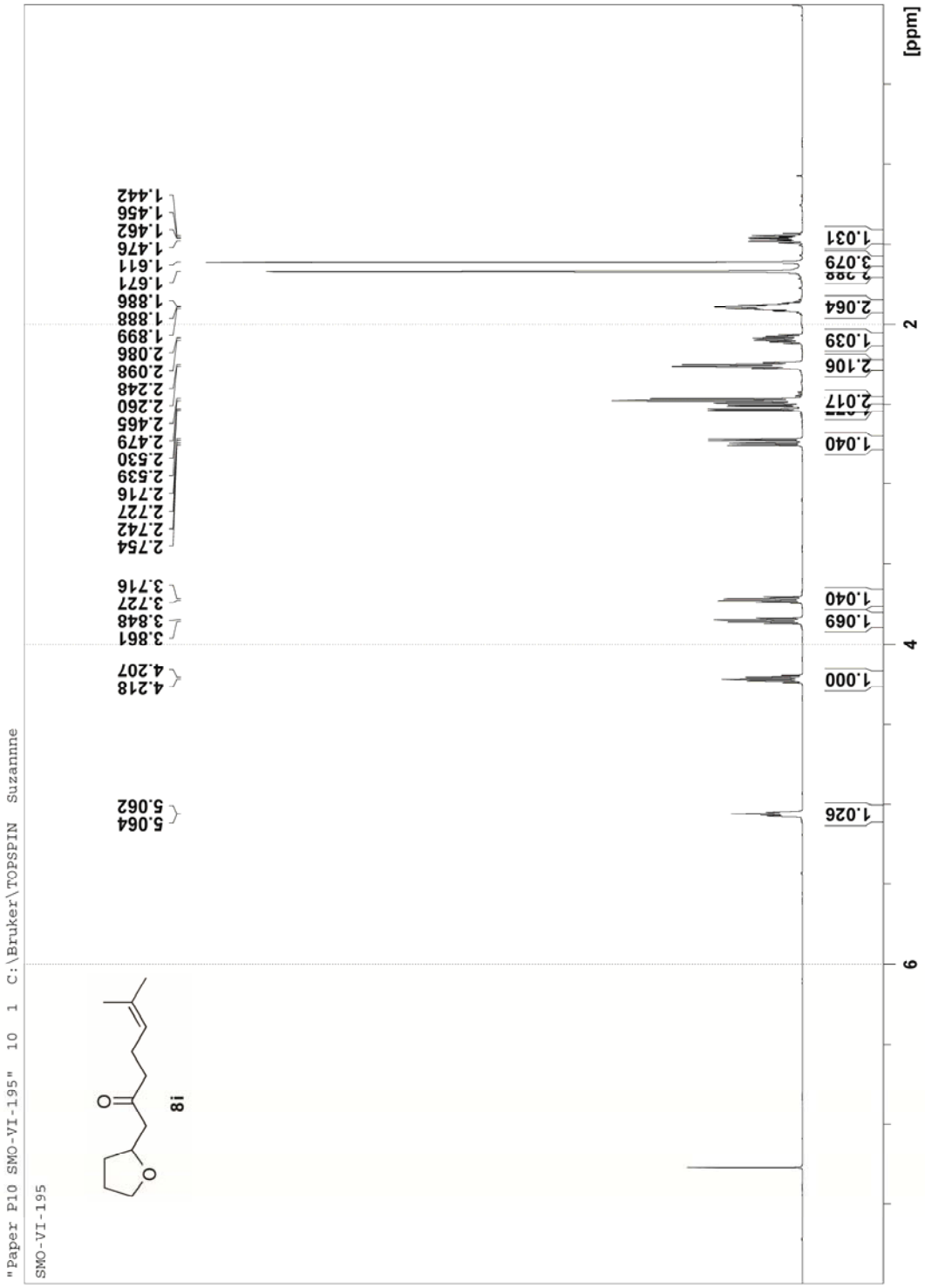
131.750
131.531
131.312
128.672
126.077
124.269
122.464
120.658
120.178
120.151
120.127
75.188
67.909
48.778
44.013
31.528
28.887
25.468
CF3
CF3
O
O
8h
0
50
100
150
200
[ppm]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SMO-VI-195
8i
5.064
5.062
4.218
4.207
3.861
3.848
3.727
3.716
2.754
2.742
2.727
2.716
2.539
2.530
2.479
2.465
2.260
2.248
2.098
2.086
1.899
1.888
1.886
1.671
1.611
1.476
1.462
1.456
1.442
1.026
1.000
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1.040
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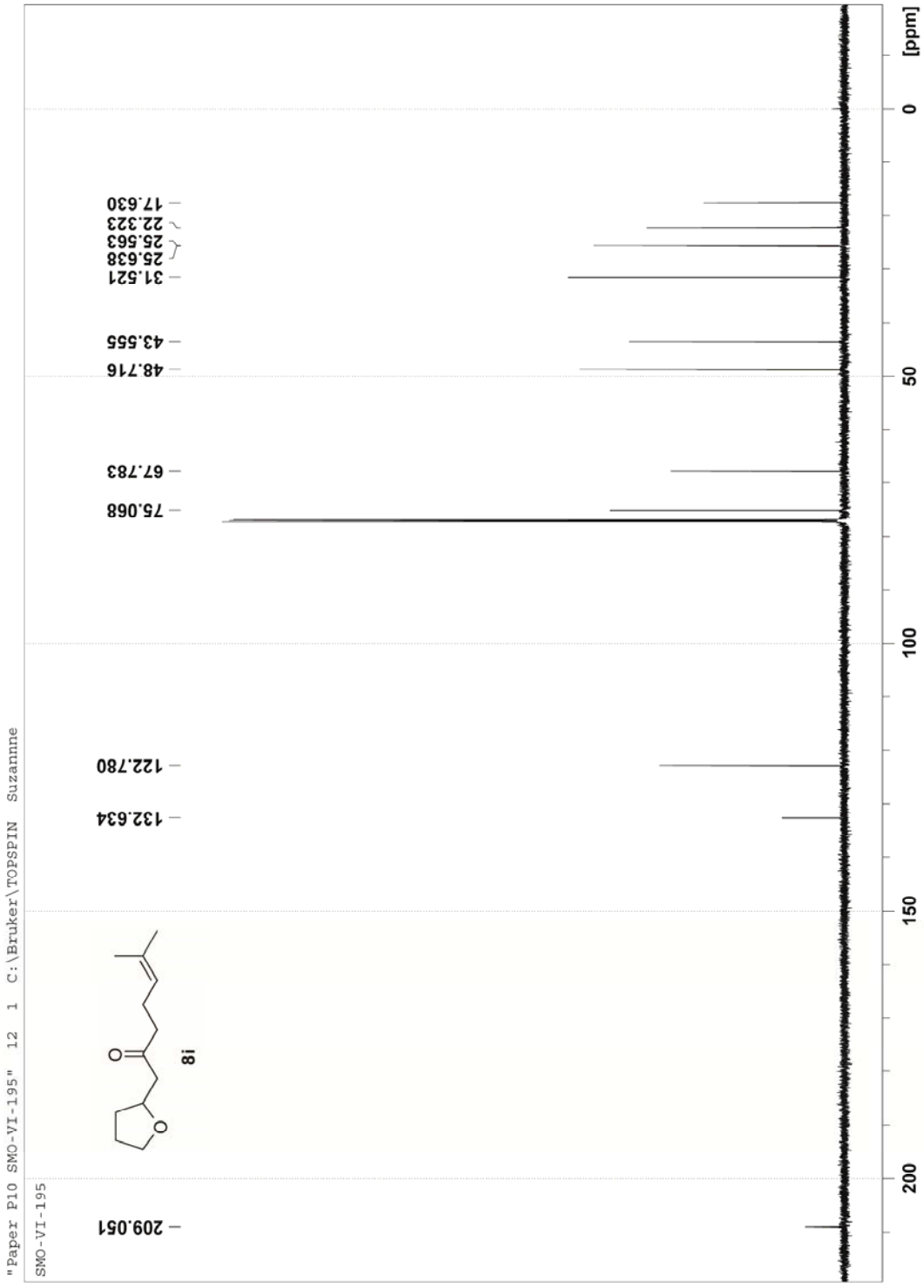
2.064
3.079
1.031
6
4
2
[ppm]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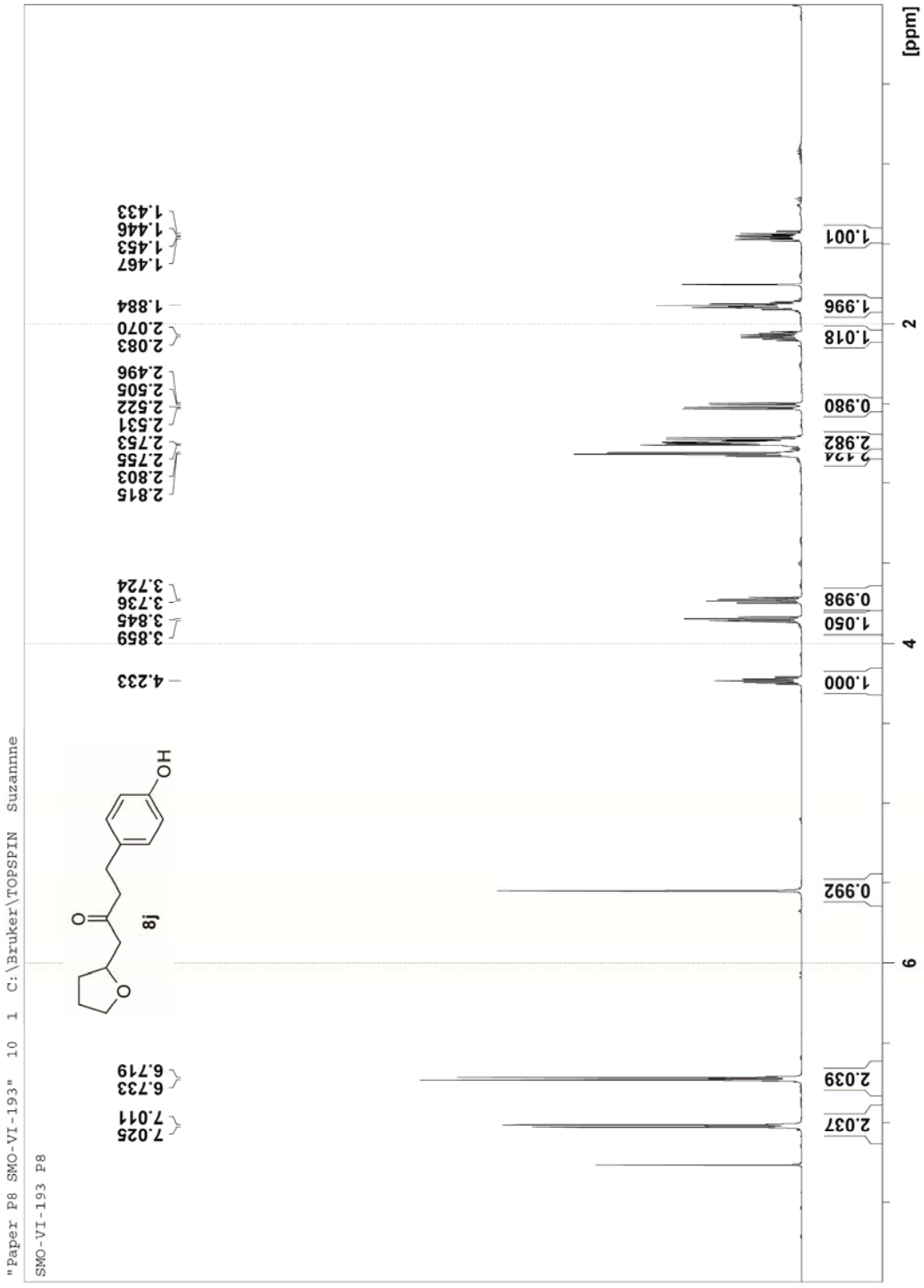
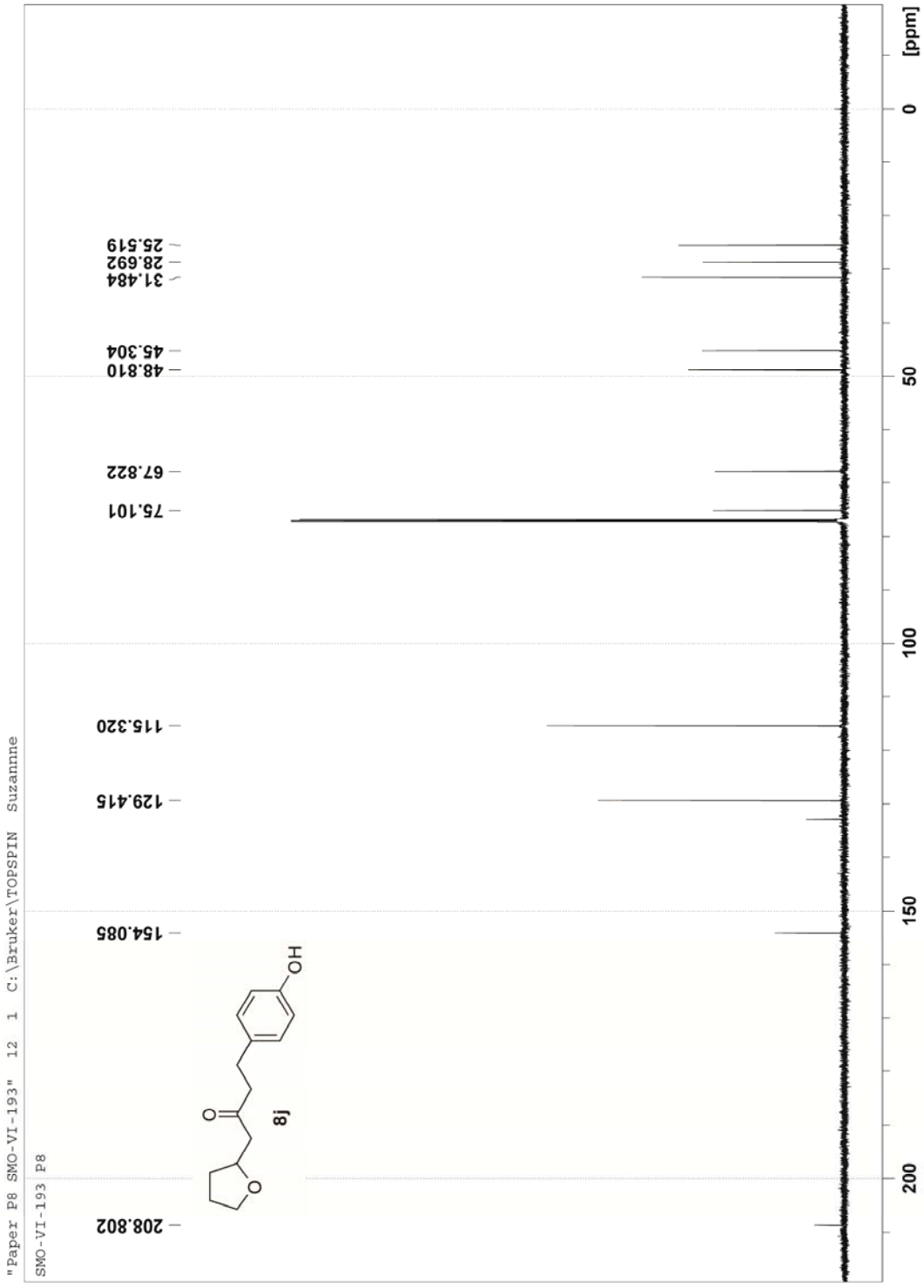
SMO-VI-195
8i
209.051
132.634
122.780
75.068
67.783
48.716
43.555
31.521
25.638
25.563
22.323
17.630
200
150
100
50
0
[ppm]


"Paper P8 SMO-VI-193" 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-193 P8
8j
OH
O
O
7.025
7.011
6.733
6.719
4.233
3.859
3.845
3.736
3.724
2.815
2.803
2.755
2.753
2.531
2.522
2.505
2.496
2.083
2.070
1.884
1.467
1.453
1.446
1.433
2.037
2.039
0.992
1.000
1.050
0.998
2.124
2.982
0.980
1.018
1.996
1.001
6
4
2
[ppm]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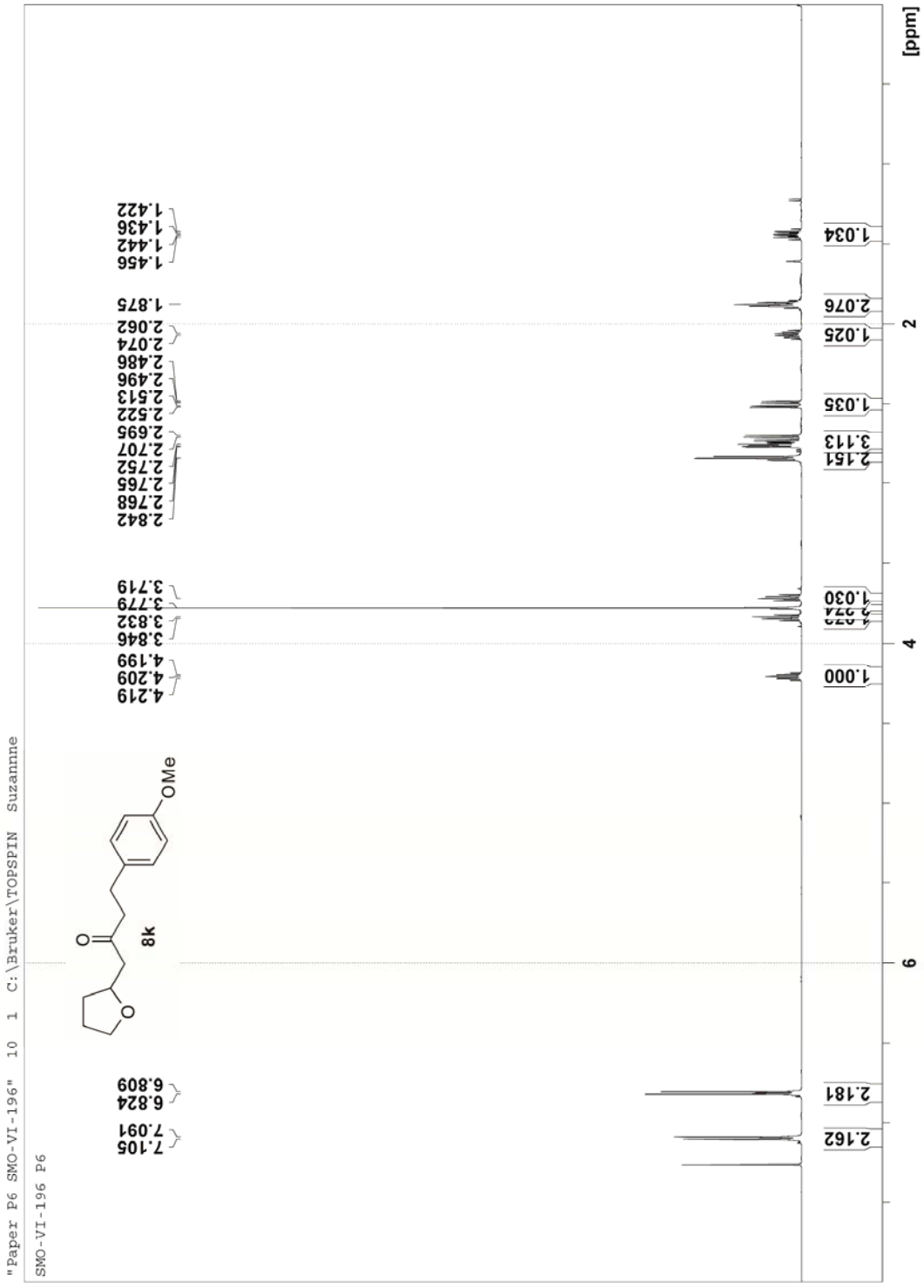
SMO-VI-193 P8
208.802
154.085
129.415
115.320
75.101
67.822
48.810
45.304
31.484
28.692
25.519
8j
OH
O
O
0
50
100
150
200
[ppm]


"Paper P6 SMO-VI-196" 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-196 P6
OMe
O
O
8k
7.105
7.091
6.824
6.809
4.219
4.209
4.199
3.846
3.832
3.779
3.719
2.842
2.768
2.765
2.752
2.707
2.695
2.522
2.513
2.496
2.486
2.074
2.062
1.875
1.456
1.442
1.436
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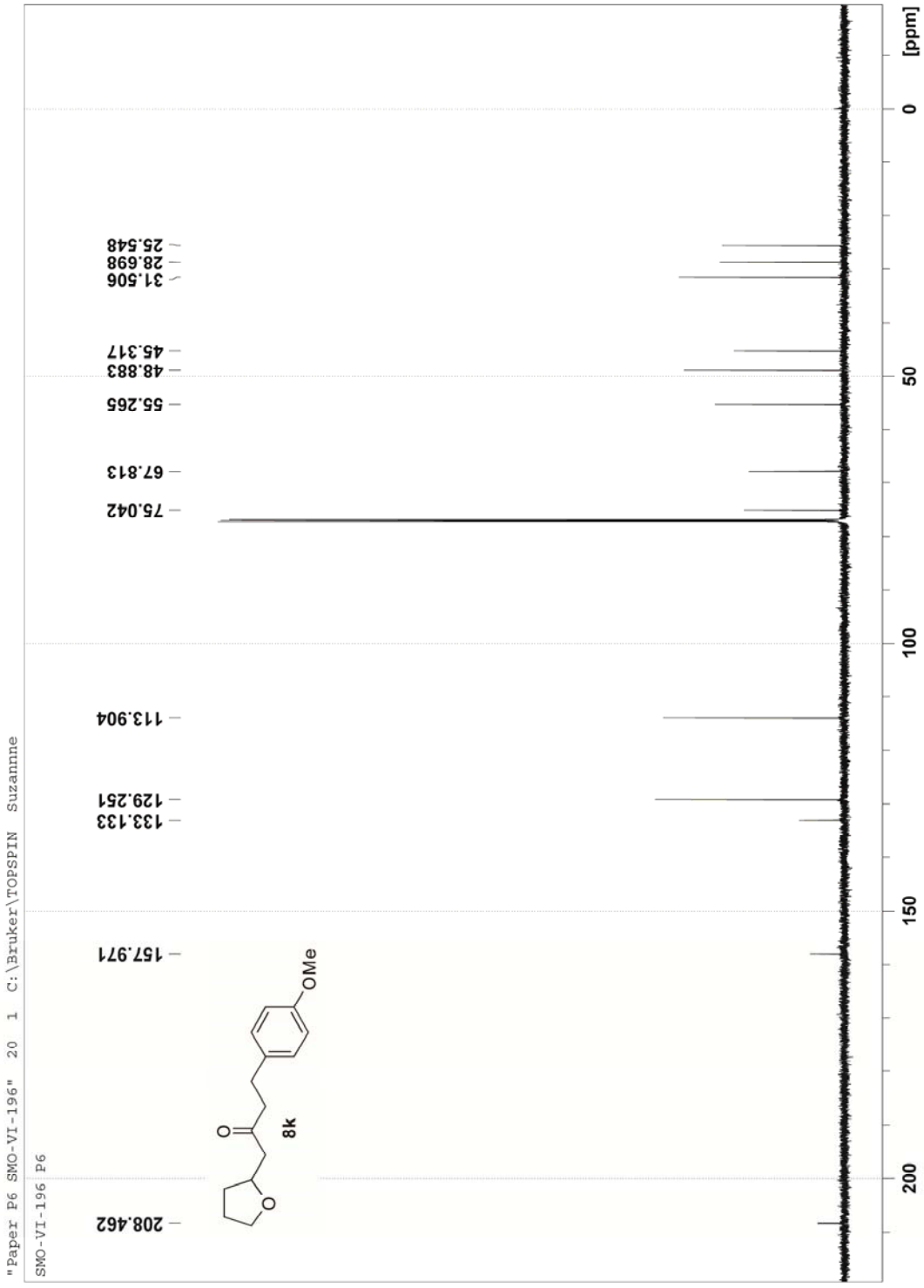
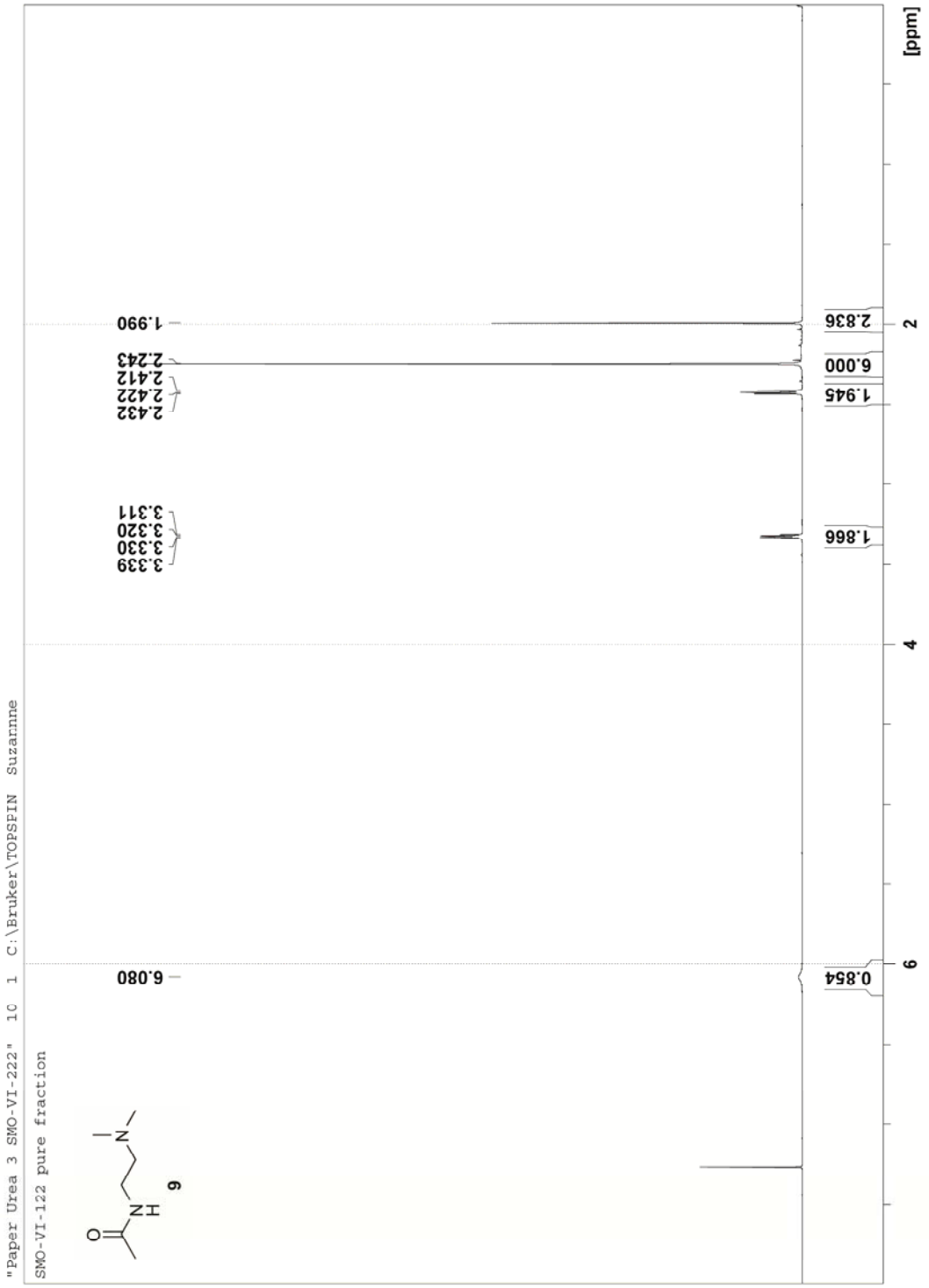
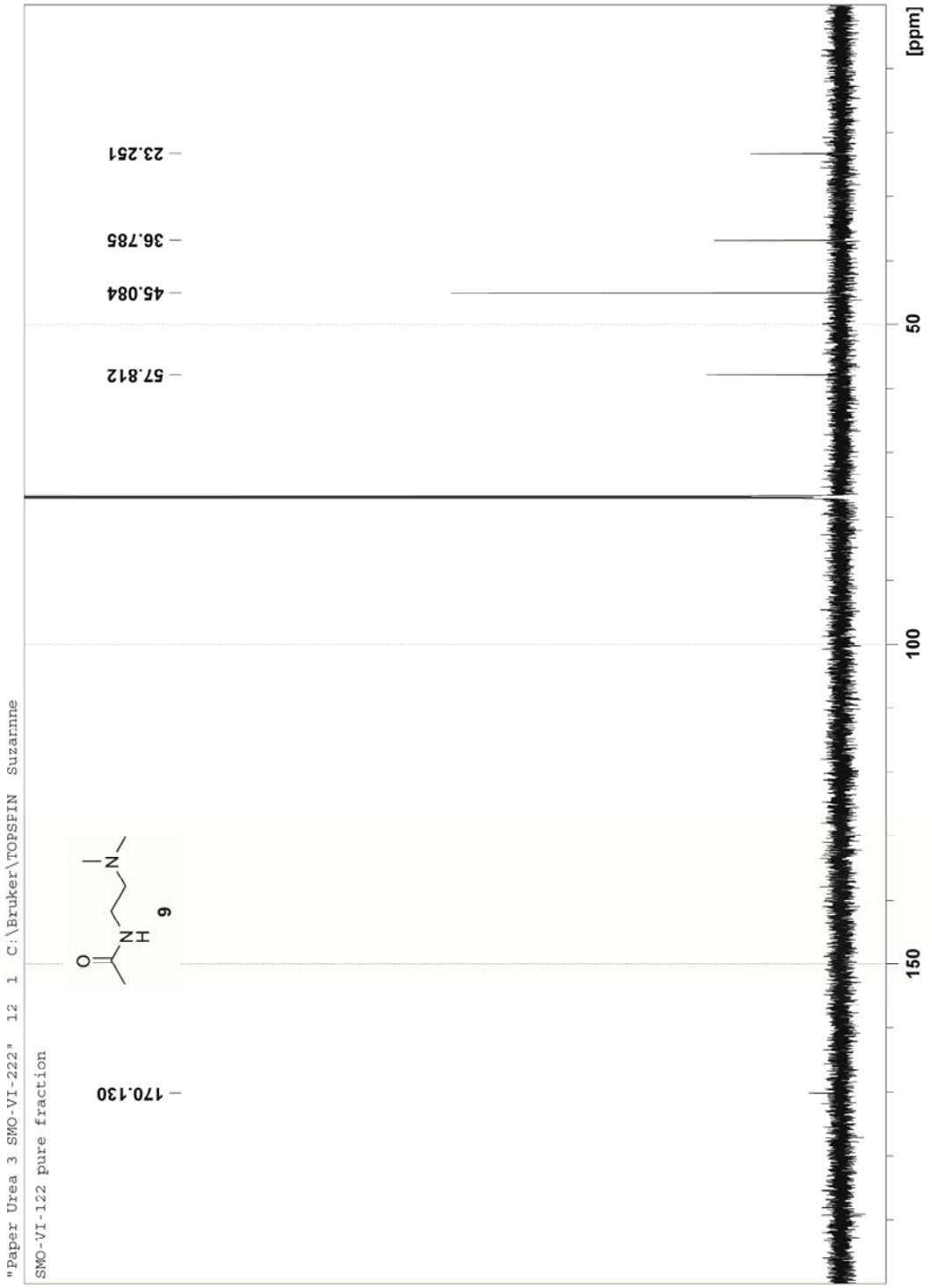
1.034
2.076
1.025
1.035
3.113
2.151
[ppm]


"Paper P6 SMO-VI-196" 20 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-196 P6
208.462
157.971
133.133
129.251
113.904
75.042
67.813
55.265
48.883
45.317
31.506
28.698
25.548
8k
OMe
O
O
[ppm]
0
50
100
150
200

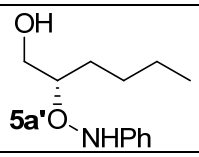

"Paper Urea 3 SMO-VI-222" 10 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-122 pure fraction
6.080
1.990
2.432
2.422
2.412
2.243
3.339
3.330
3.320
3.311
0.854
2.836
6.000
1.945
1.866
6
4
2
[ppm]


"Paper Urea 3 SMO-VI-222" 12 1 C:\Bruker\TOPSPIN Suzanne
SMO-VI-122 pure fraction
170.130
57.812
45.084
36.785
23.251
6
9
150
100
50
[ppm]

APPENDIX 2

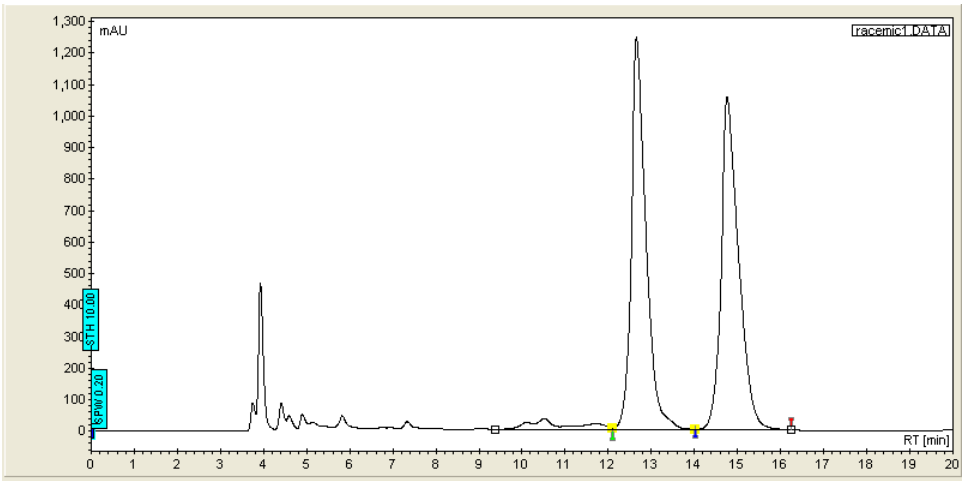
Supporting Information for Chapter 3

1. Chromatograms of Racemic and Enantiomerically Enriched Products



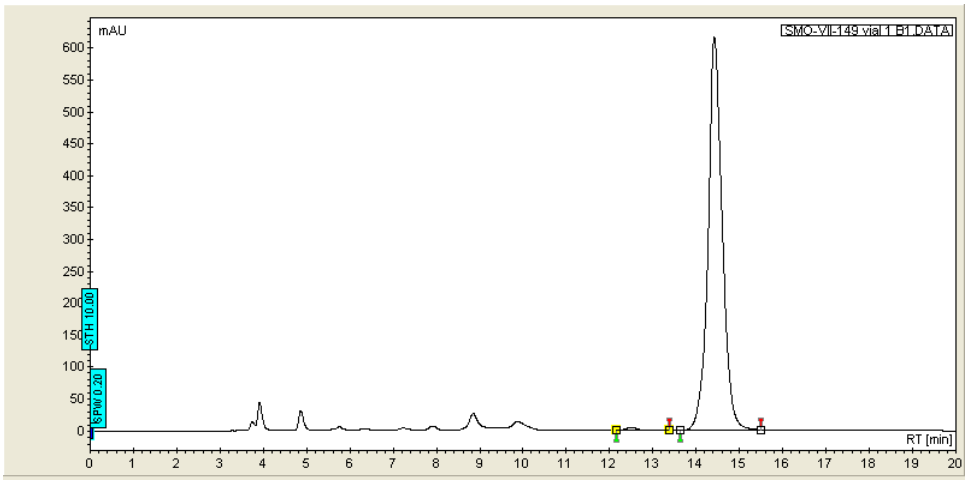
Method: CHIRALPAK IA and guard column 95% hex 5% ipa, 1.00 ml/min, 254 nm

Racemic

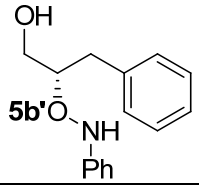


#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12.65	49.60	1244.5	489.5	49.597
2	UNKNOWN	14.76	50.40	1054.6	497.4	50.403
Total			100.00	2299.1	986.9	100.000

Enantioenriched – 99% ee

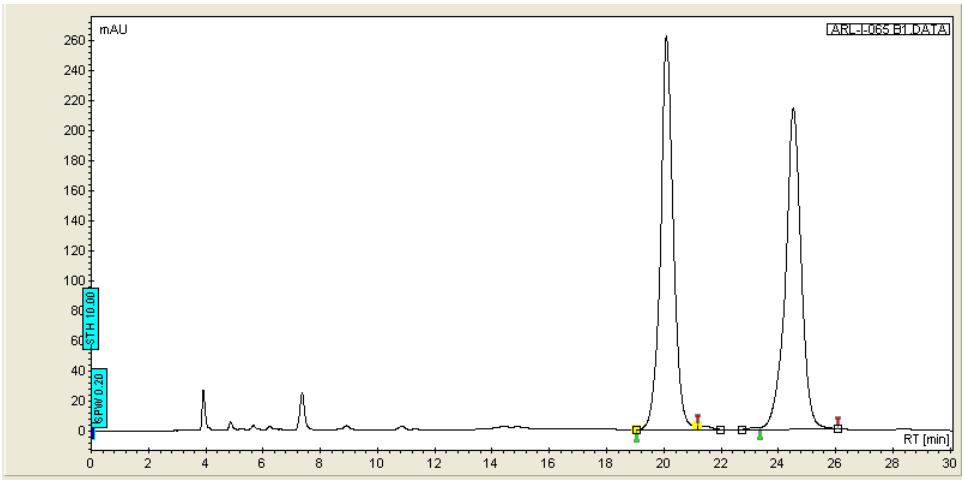


#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12.50	0.68	4.9	1.6	0.678
2	UNKNOWN	14.42	99.32	615.7	234.4	99.322
Total			100.00	620.6	236.0	100.000



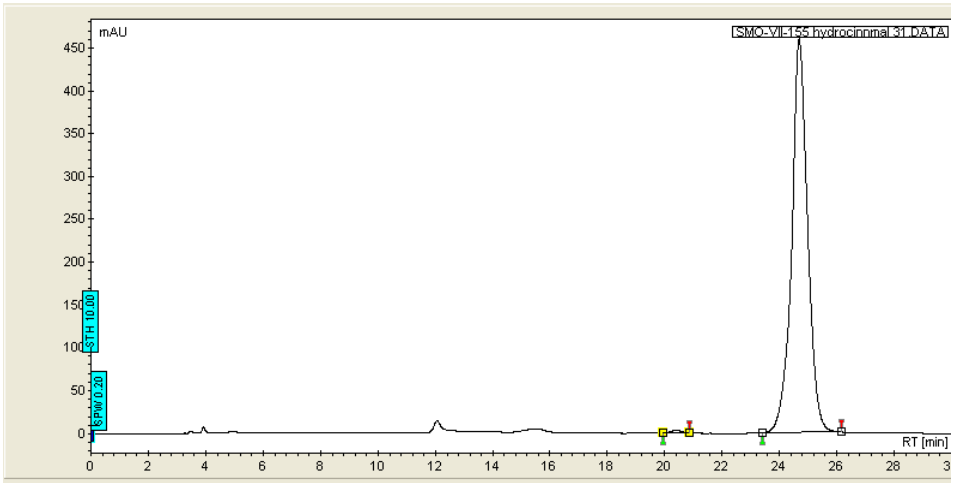
Method: CHIRALPAK IA and guard column 95% hex 5% ipa, 1.00 ml/min, 254 nm

Racemic

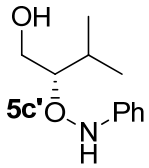


#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20.09	49.81	262.3	135.7	49.813
2	UNKNOWN	24.53	50.19	214.3	136.7	50.187
Total			100.00	476.6	272.3	100.000

Enantioenriched – 99% ee

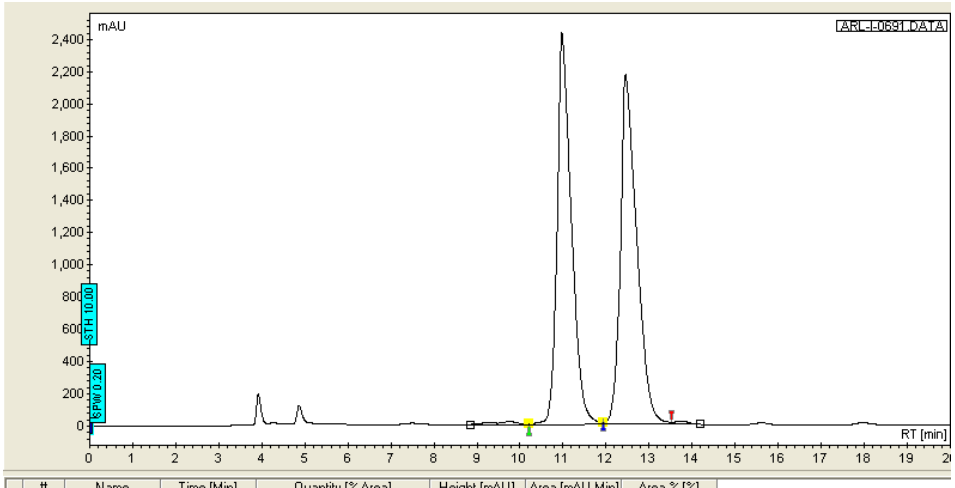


#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20.41	0.44	3.1	1.3	0.436
2	UNKNOWN	24.69	99.56	459.5	296.0	99.564
Total			100.00	462.6	297.3	100.000



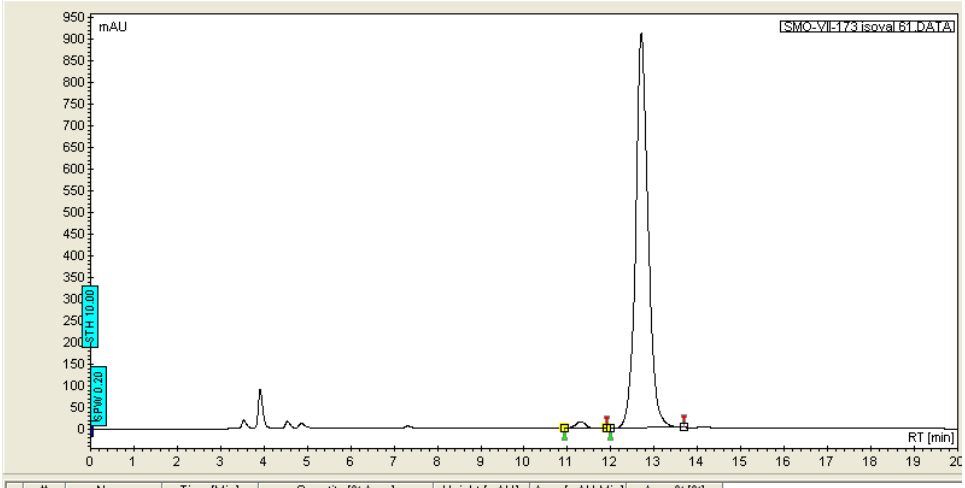
Method: CHIRALPAK IA and guard column 95% hex 5% ipa, 1.00 ml/min, 254 nm

Racemic



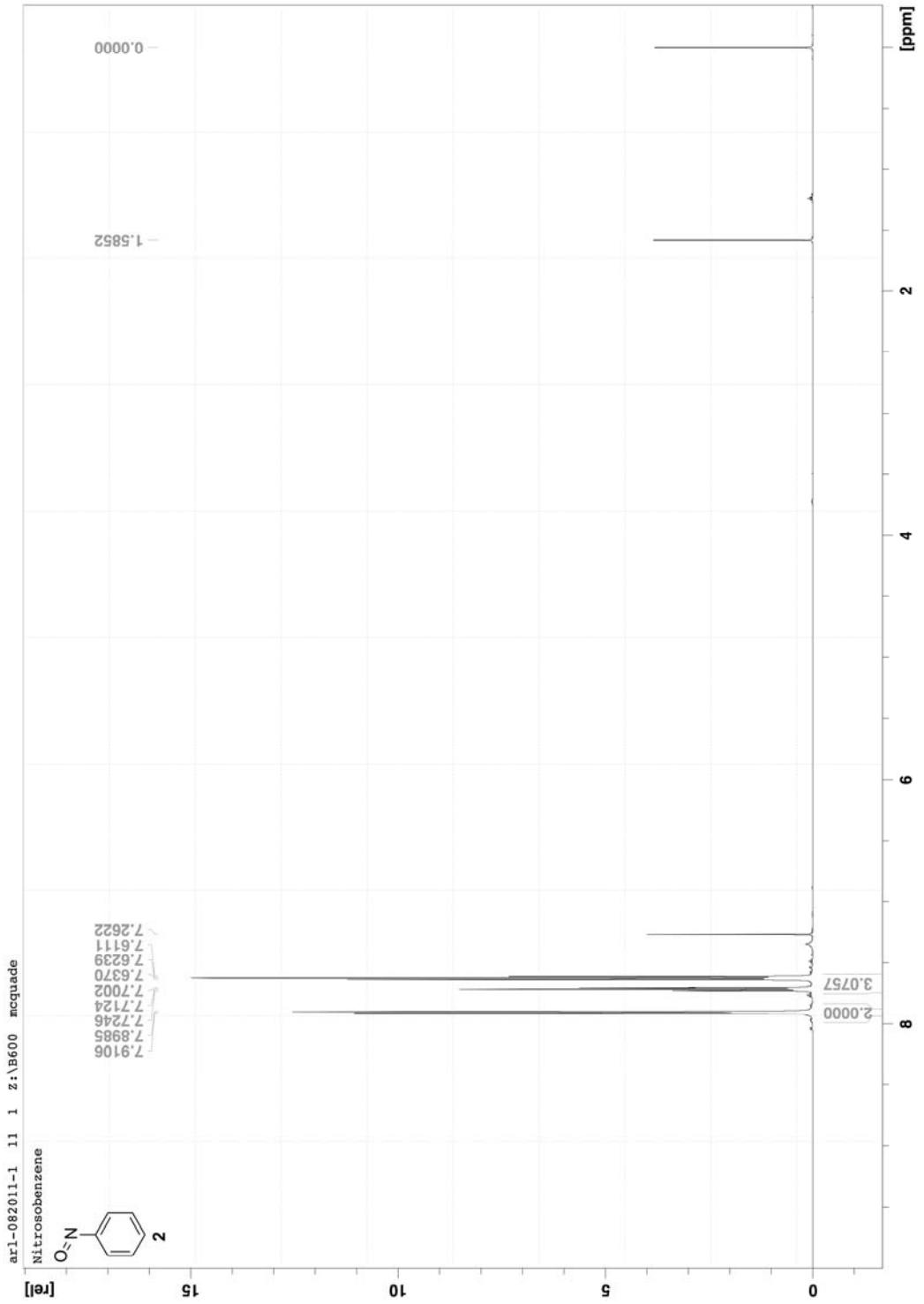
#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.97	49.25	2432.7	931.7	49.254
2	UNKNOWN	12.45	50.75	2172.2	959.9	50.746
Total			100.00	4604.9	1891.7	100.000

Enantioenriched – 97% ee



#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	11.31	1.36	15.4	4.2	1.359
2	UNKNOWN	12.70	98.64	912.1	303.8	98.641
Total			100.00	927.4	308.0	100.000

2. ^{1}H and ^{13}C NMR Spectra of Chemical Compounds



arl-082411-2 12 1 2:\B600 mcguade
Nitrosobenzene
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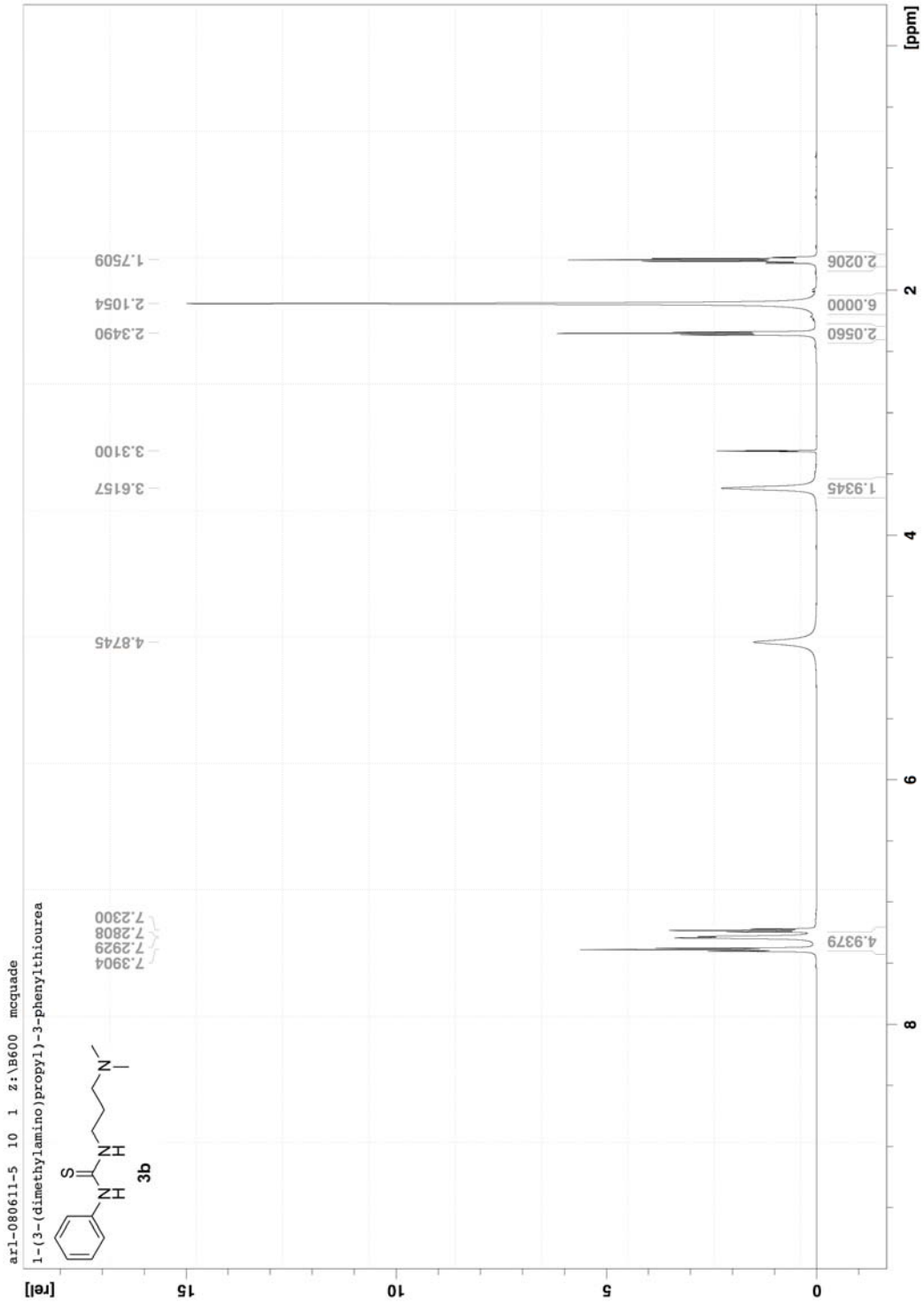
135.7254
129.4818
121.1062
77.4394
77.2281
77.0164
[rel]
[ppm]


arl-080611-5 10 1 2:\B600 mcquade
1-(3-(dimethylamino)propyl)-3-phenylthiourea
3b
[rel]
15
10
5
0
[ppm]
8
6
4
2
7.3904
7.2929
7.2808
7.2300
4.8745
3.6157
3.3100
2.3490
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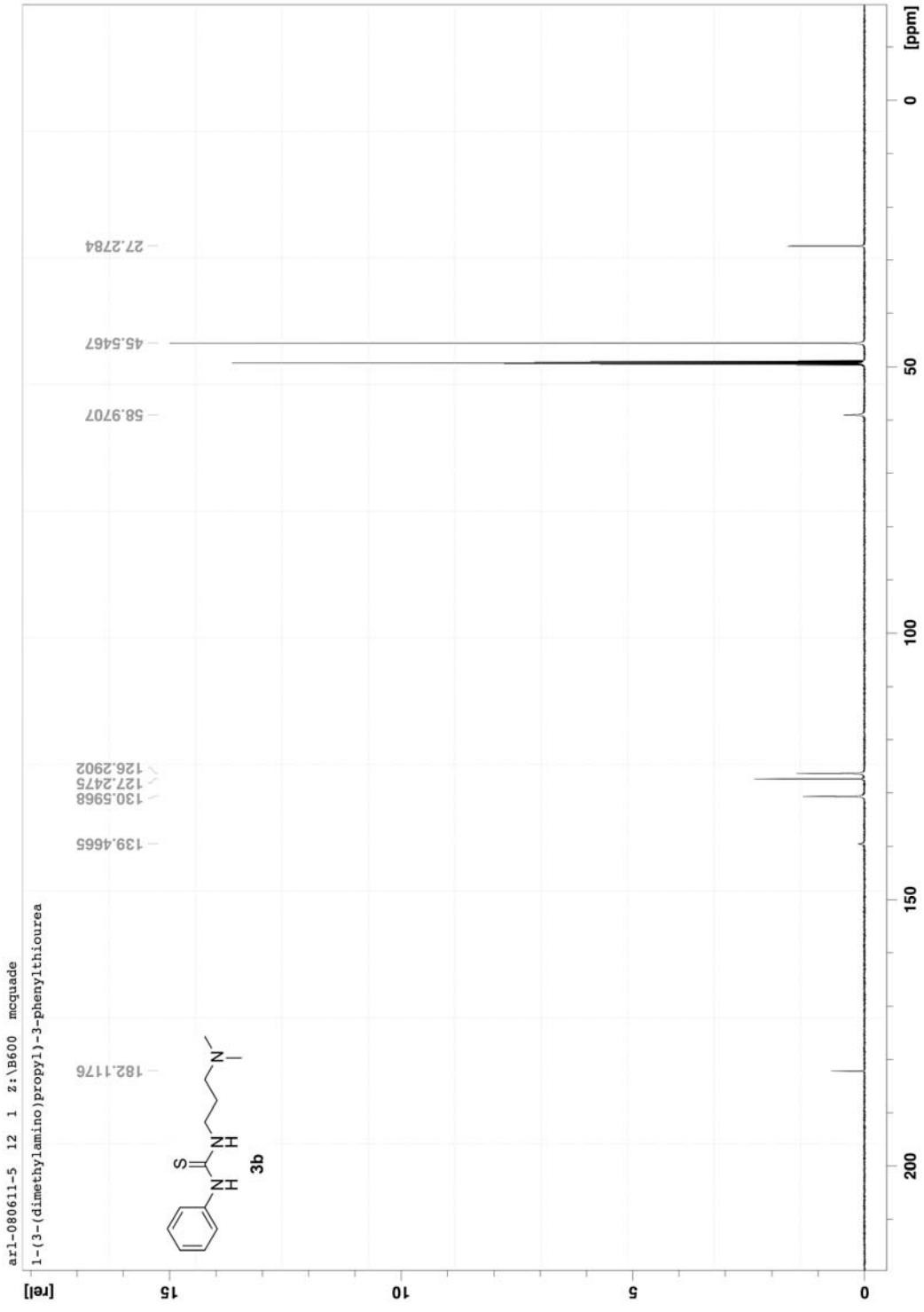
4.9379
1.9345
2.0560
6.0000
2.0206


arl-080611-5 12 1 2:\B600 mcquade
1-(3-(dimethylamino)propyl)-3-phenylthiourea
[rel]
15
10
5
0
[ppm]
200
150
100
50
0
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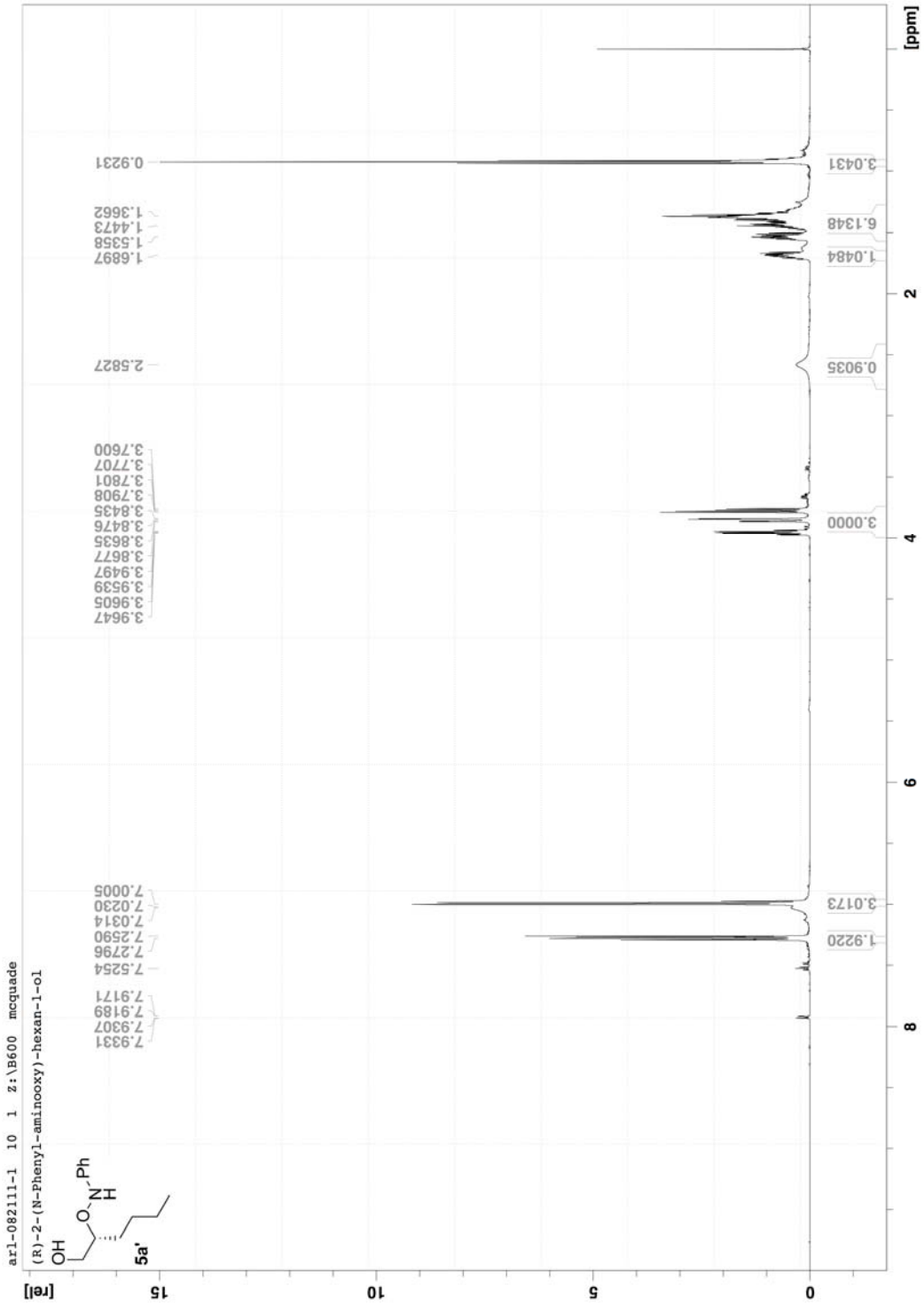
127.2475
126.2902
58.9707
45.5467
27.2784
3b


arl-082111-1 10 1 2:\B600 mcquade
(R)-2-(N-Phenyl-aminooxy)-hexan-1-ol
5a'
OH
O
N
H
Ph
[rel]
[ppm]
7.9331
7.9307
7.9189
7.9171
7.5254
7.2796
7.2590
7.0314
7.0230
7.0005
3.9647
3.9605
3.9539
3.9497
3.8677
3.8635
3.8476
3.8435
3.7908
3.7801
3.7707
3.7600
2.5827
1.6897
1.5358
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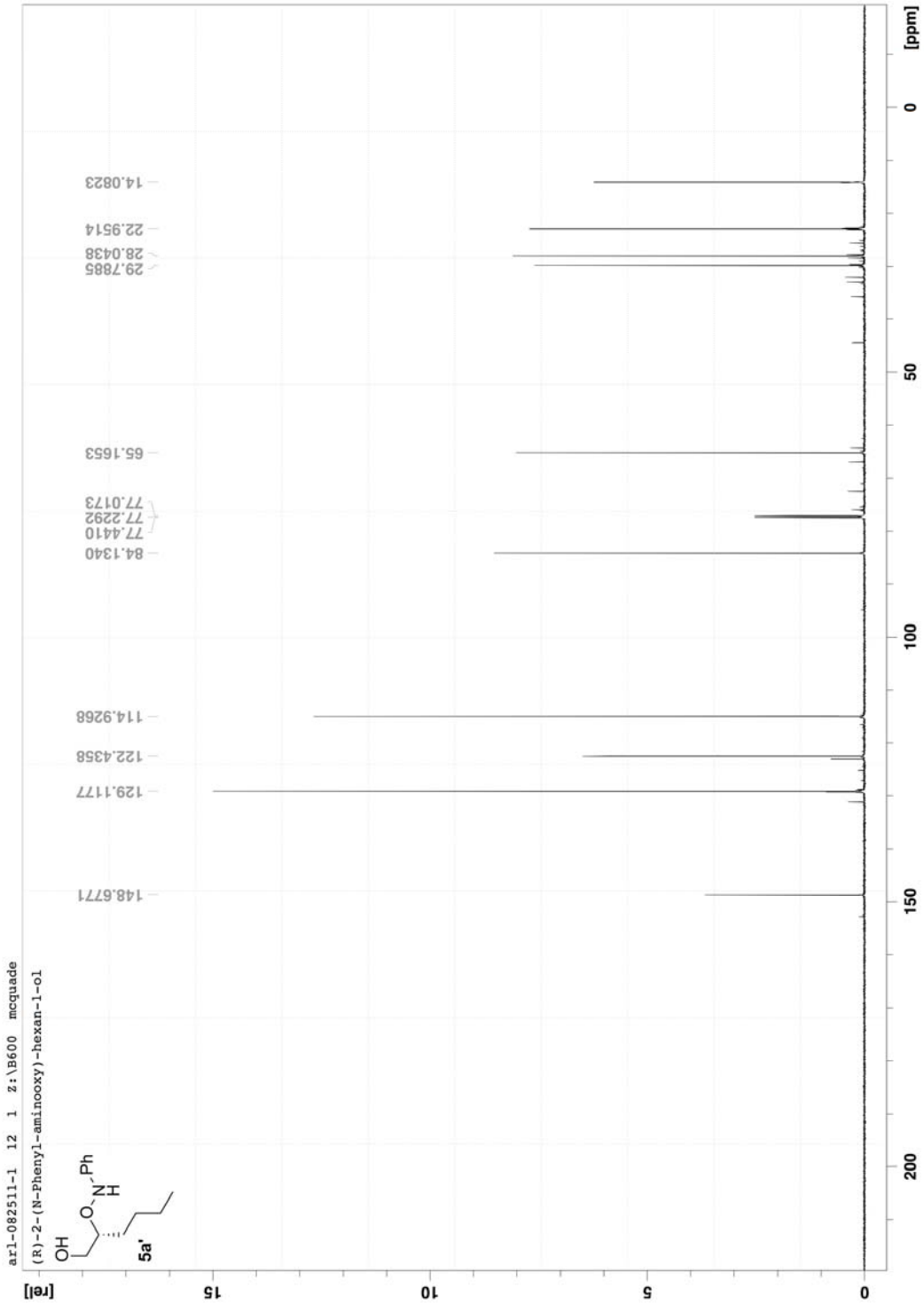
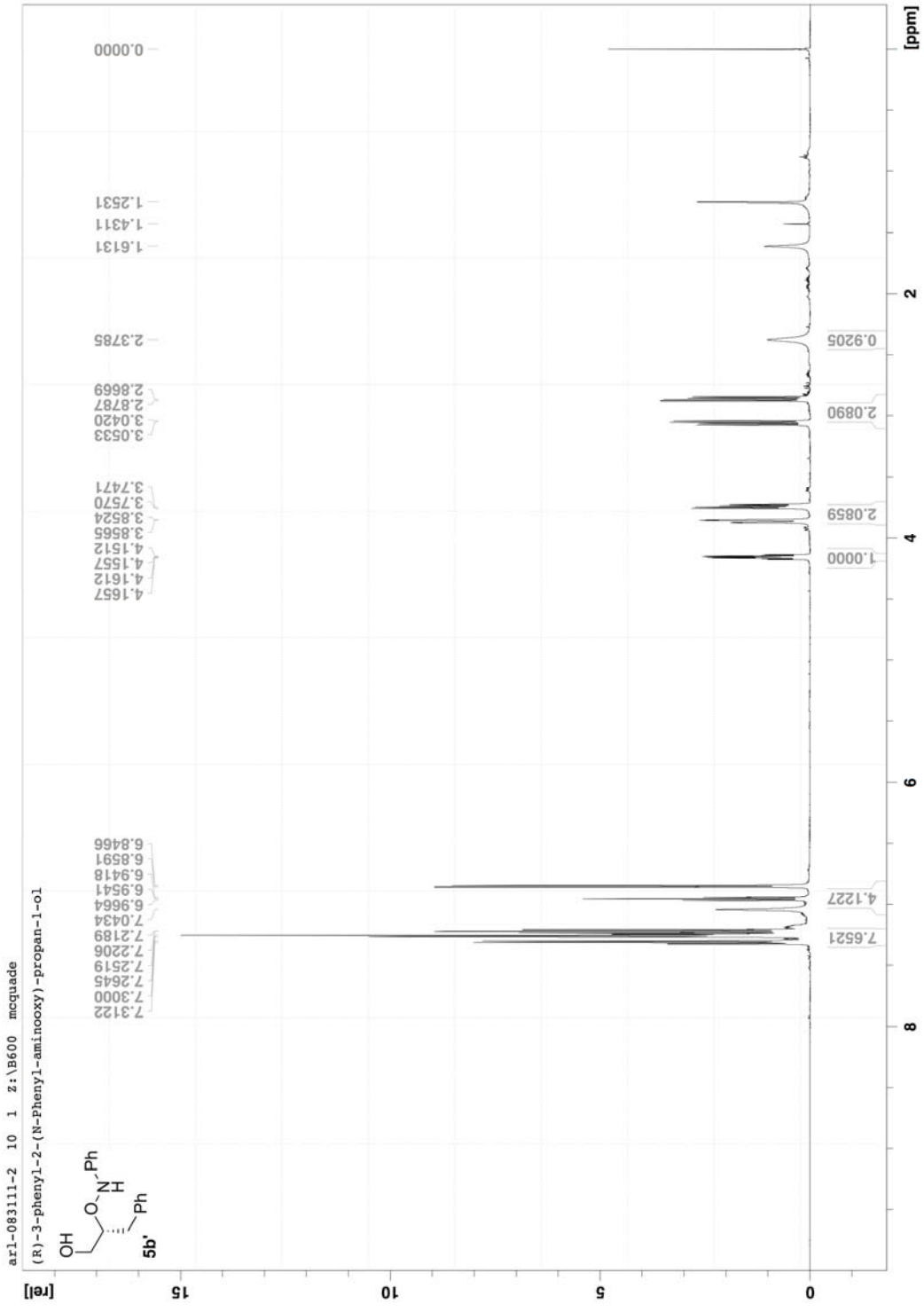
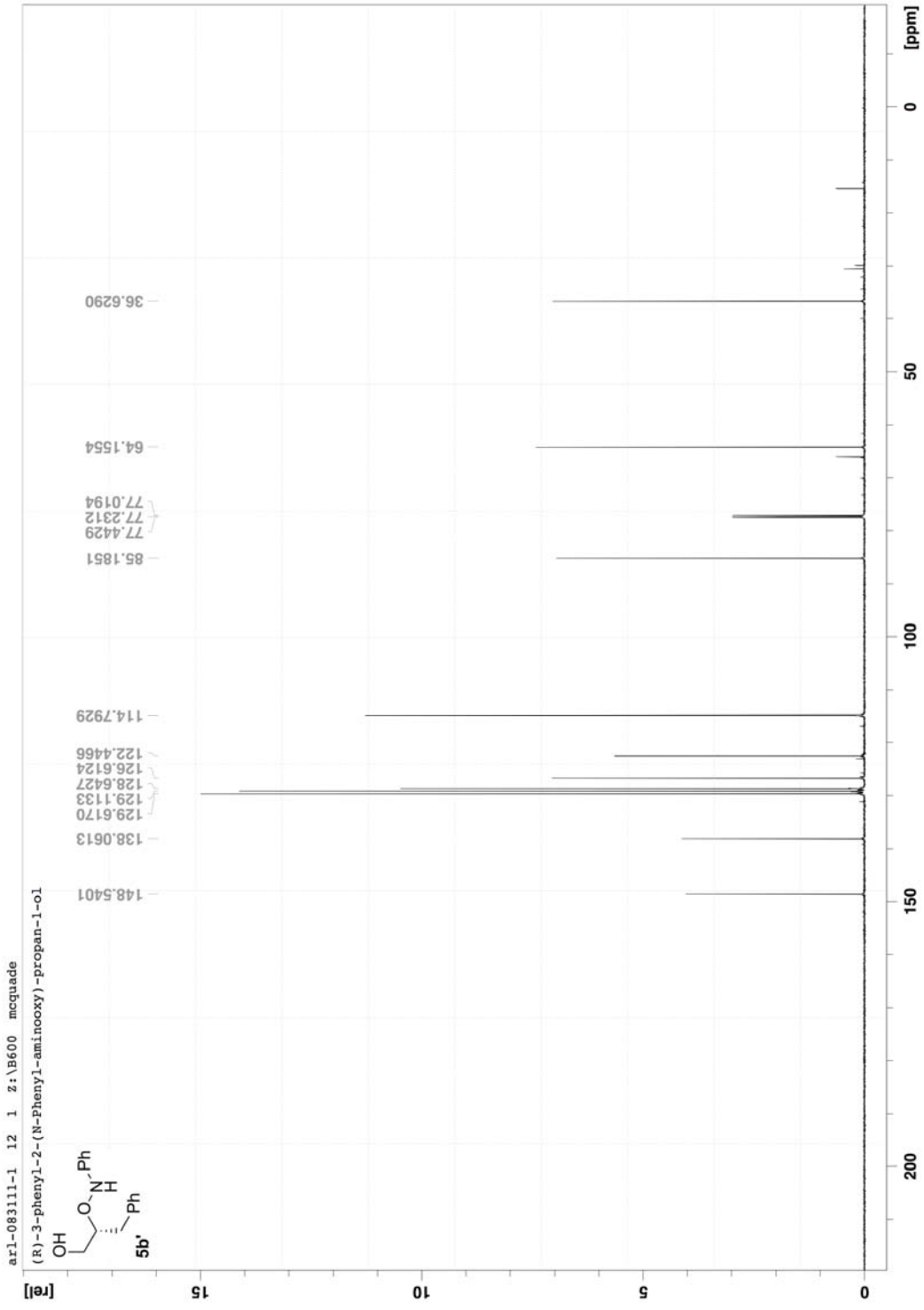
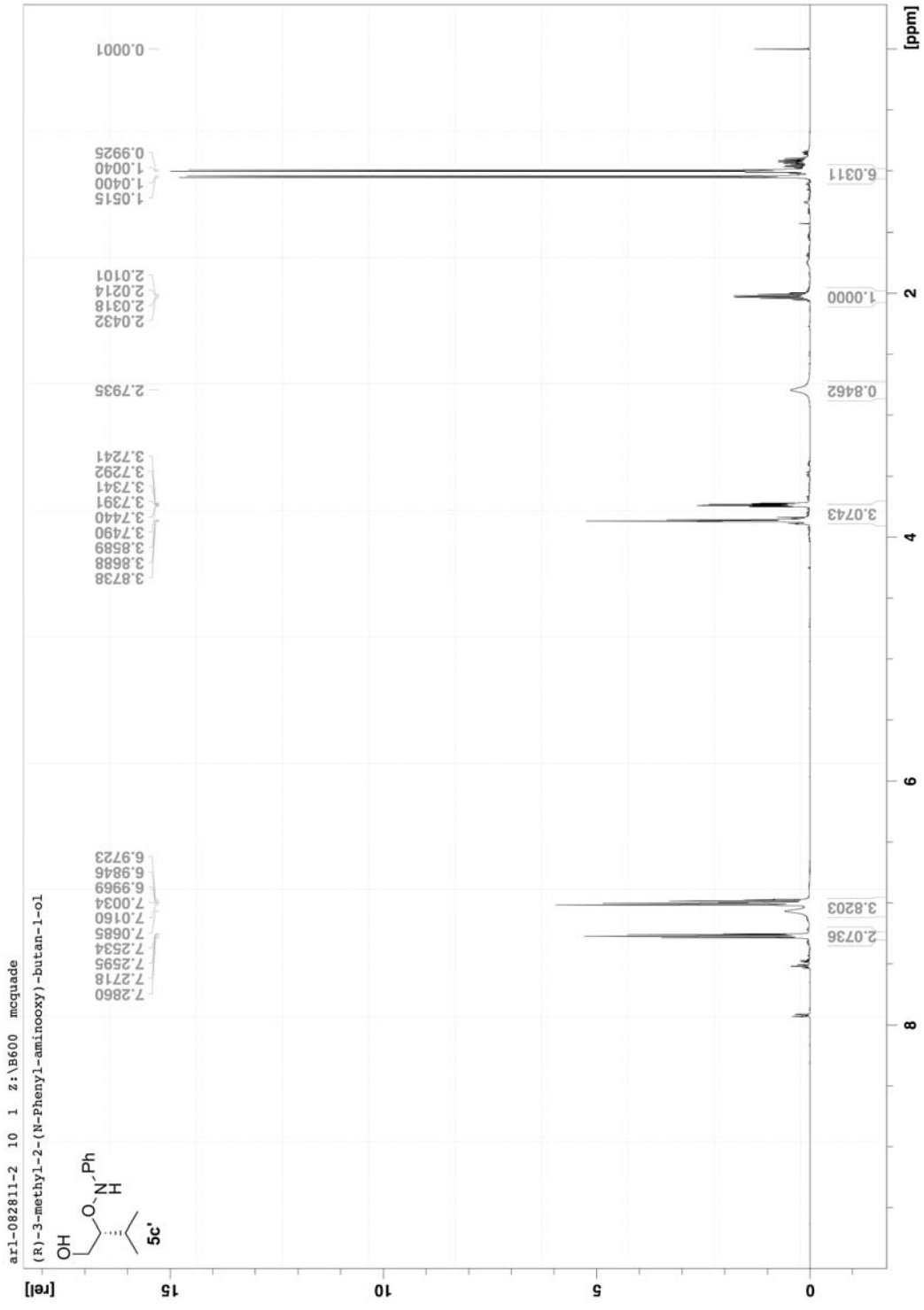
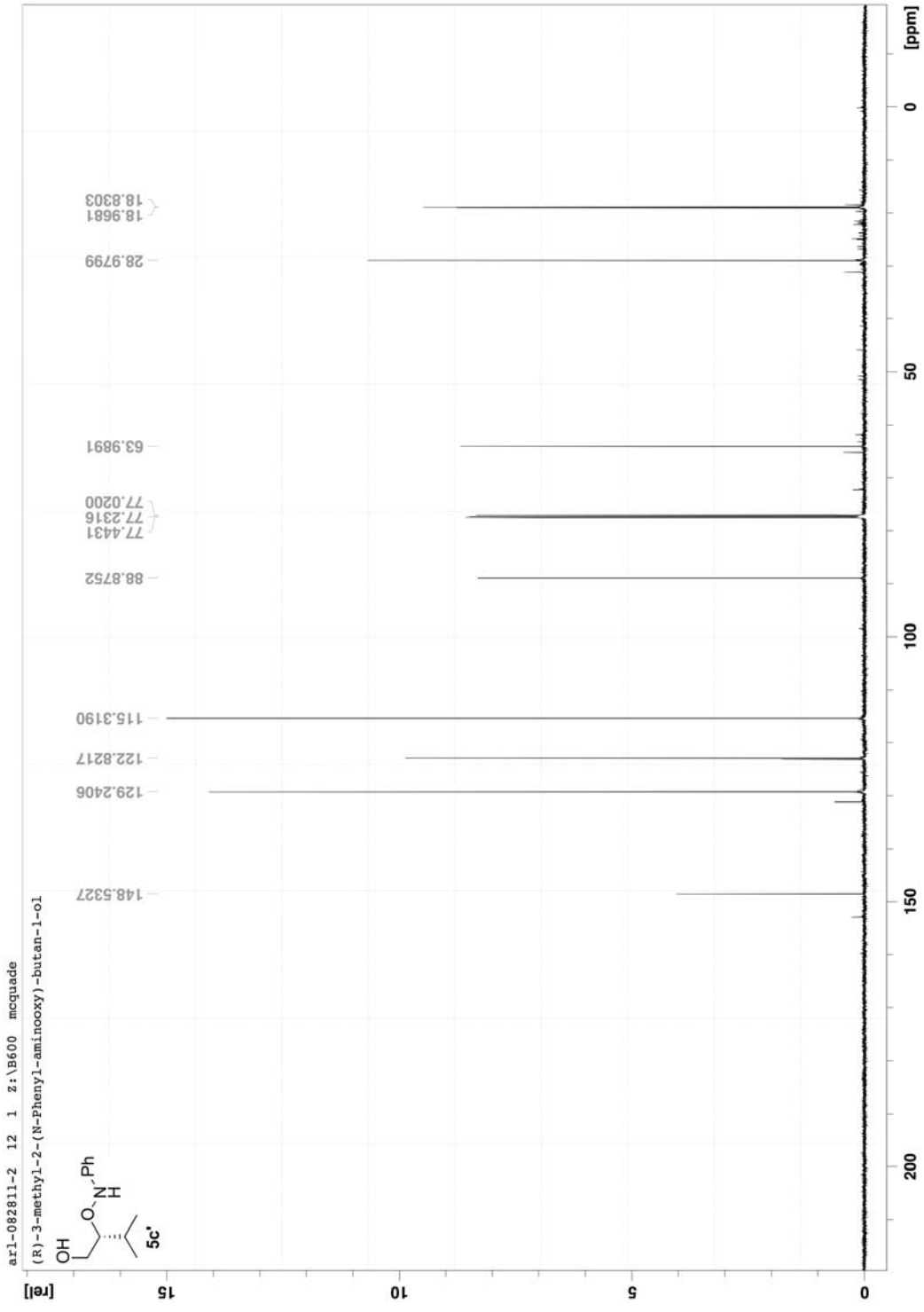
0.9035
1.0484
6.1348
3.0431

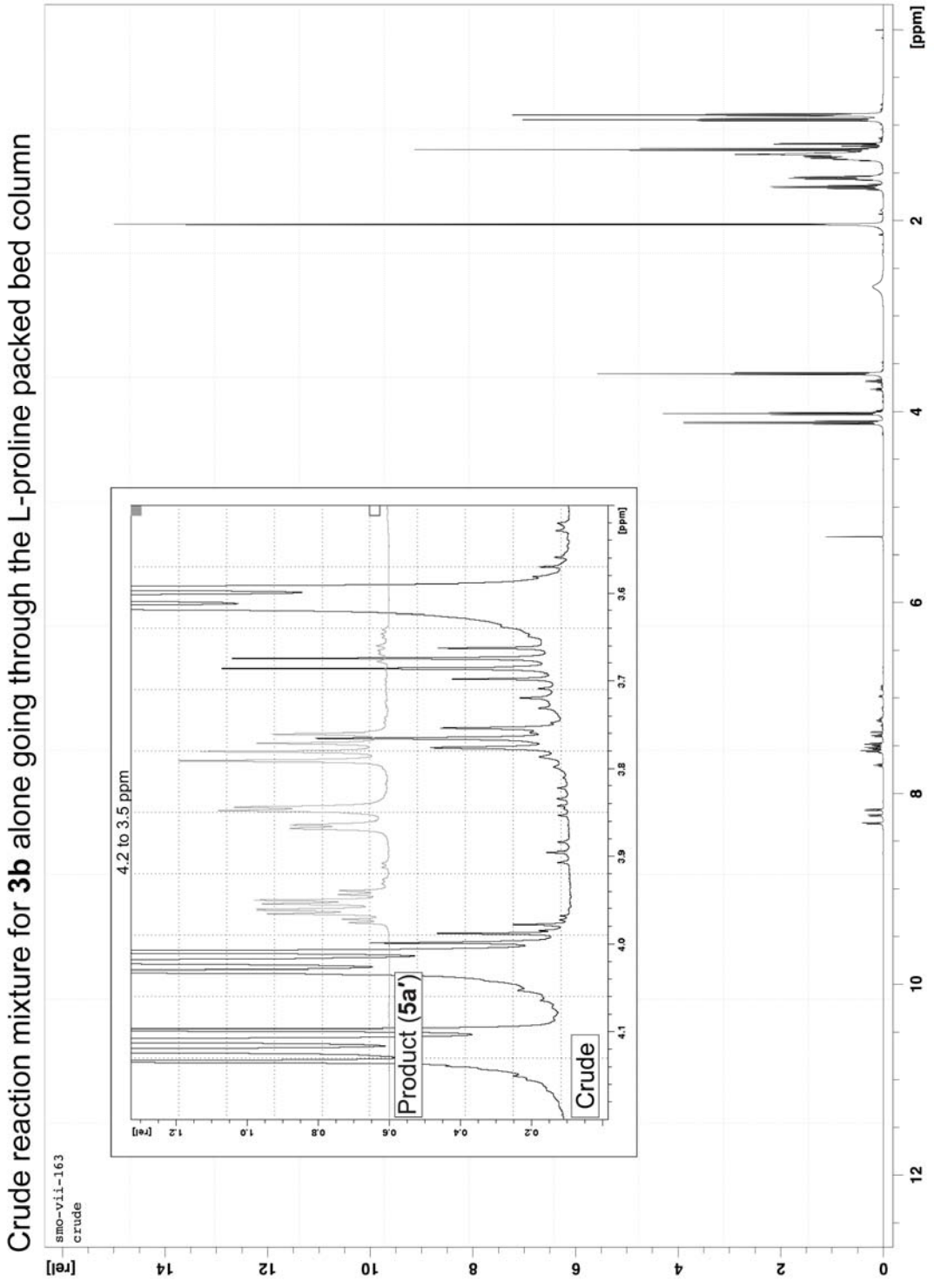

arl-082511-1 12 1 2:\B600 mcguade
(R)-2-(N-Phenyl-aminooxy)-hexan-1-ol
5a'
148.6771
129.1177
122.4358
114.9268
84.1340
77.4410
77.2292
77.0173
65.1653
29.7885
28.0438
22.9514
14.0823
[rel]
[ppm]

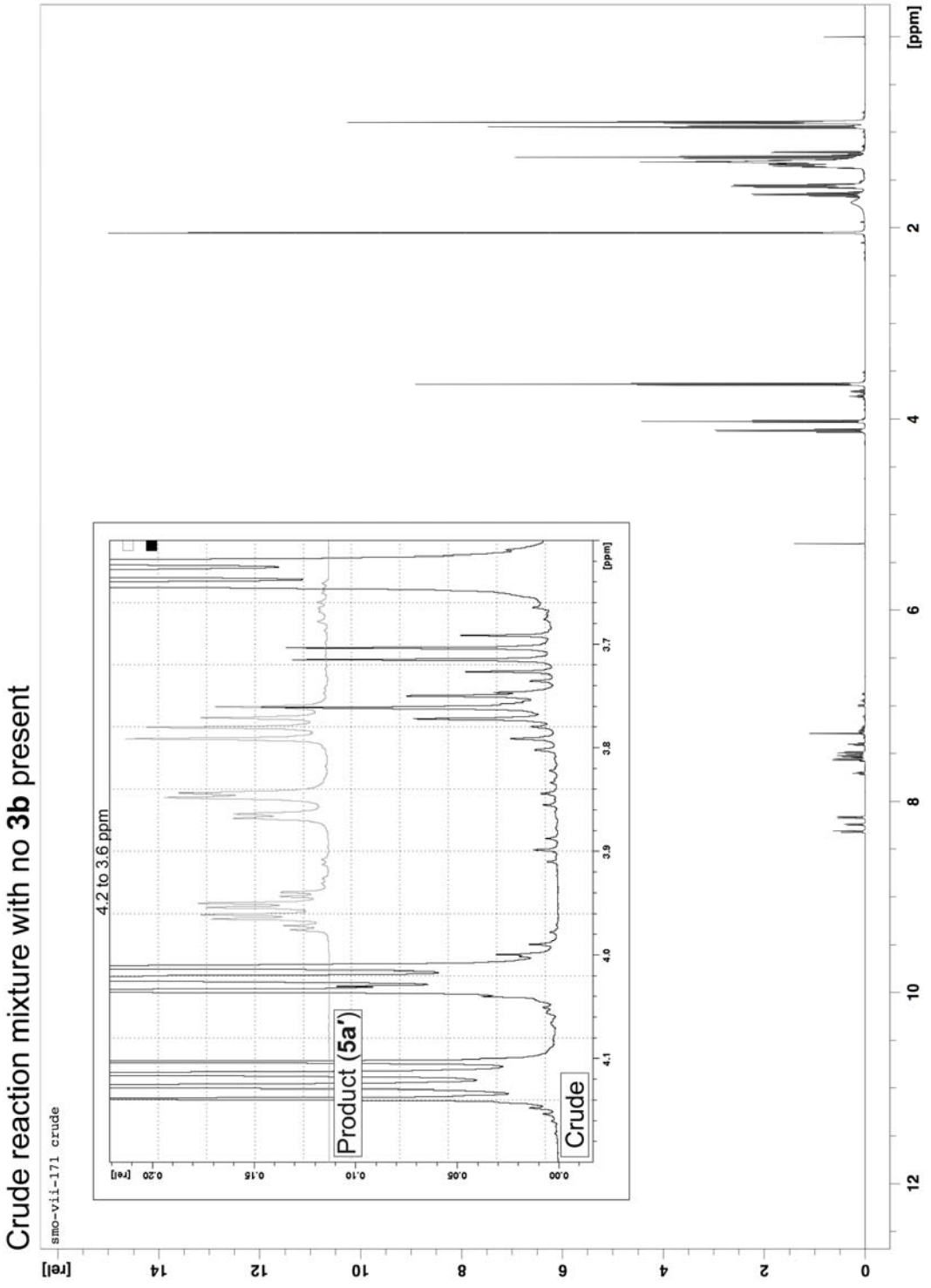

arl-083111-2 10 1 2:\B600 mcquade
(R)-3-phenyl-2-(N-Phenyl-aminooxy)-propan-1-ol
5b'
OH
O
N
H
Ph
Ph
[rel]
[ppm]
0.0000
1.2531
1.4311
1.6131
2.3785
2.8669
2.8787
3.0420
3.0533
3.7471
3.7570
3.8524
3.8565
4.1512
4.1557
4.1612
4.1657
6.8466
6.8591
6.9418
6.9541
6.9664
7.0434
7.2189
7.2206
7.2519
7.2645
7.3000
7.3122
7.6521
4.1227
2.0859
1.0000
2.0890
0.9205


arl-083111-1 12 1 z:\B600 mcquade
(R)-3-phenyl-2-(N-Phenyl-aminooxy)-propan-1-ol
5b'
148.5401
138.0613
129.6170
129.1133
128.6427
126.6124
122.4466
114.7929
85.1851
77.4429
77.2312
77.0194
64.1554
36.6290
[rel]
[ppm]


arl-082811-2 10 1 2:\B600 mcquade
(R)-3-methyl-2-(N-Phenyl-aminooxy)-butan-1-ol
5c'
[rel]
[ppm]
0.0001
1.0515
1.0400
1.0040
0.9925
2.0432
2.0318
2.0214
2.0101
2.7935
3.7241
3.7292
3.7341
3.7391
3.7440
3.7490
3.8589
3.8688
3.8738
6.9723
6.9846
6.9969
7.0034
7.0160
7.0685
7.2534
7.2595
7.2718
7.2860
2.0736
3.8203
6.0311
1.0000
0.8462
3.0743


arl-082811-2 12 1 2:\B600 mcquade
(R)-3-methyl-2-(N-Phenyl-aminooxy)-butan-1-ol
5c'
[rel]
[ppm]
148.5327
129.2406
122.8217
115.3190
88.8752
77.4431
77.2316
77.0200
63.9891
28.9799
18.9681
18.8303

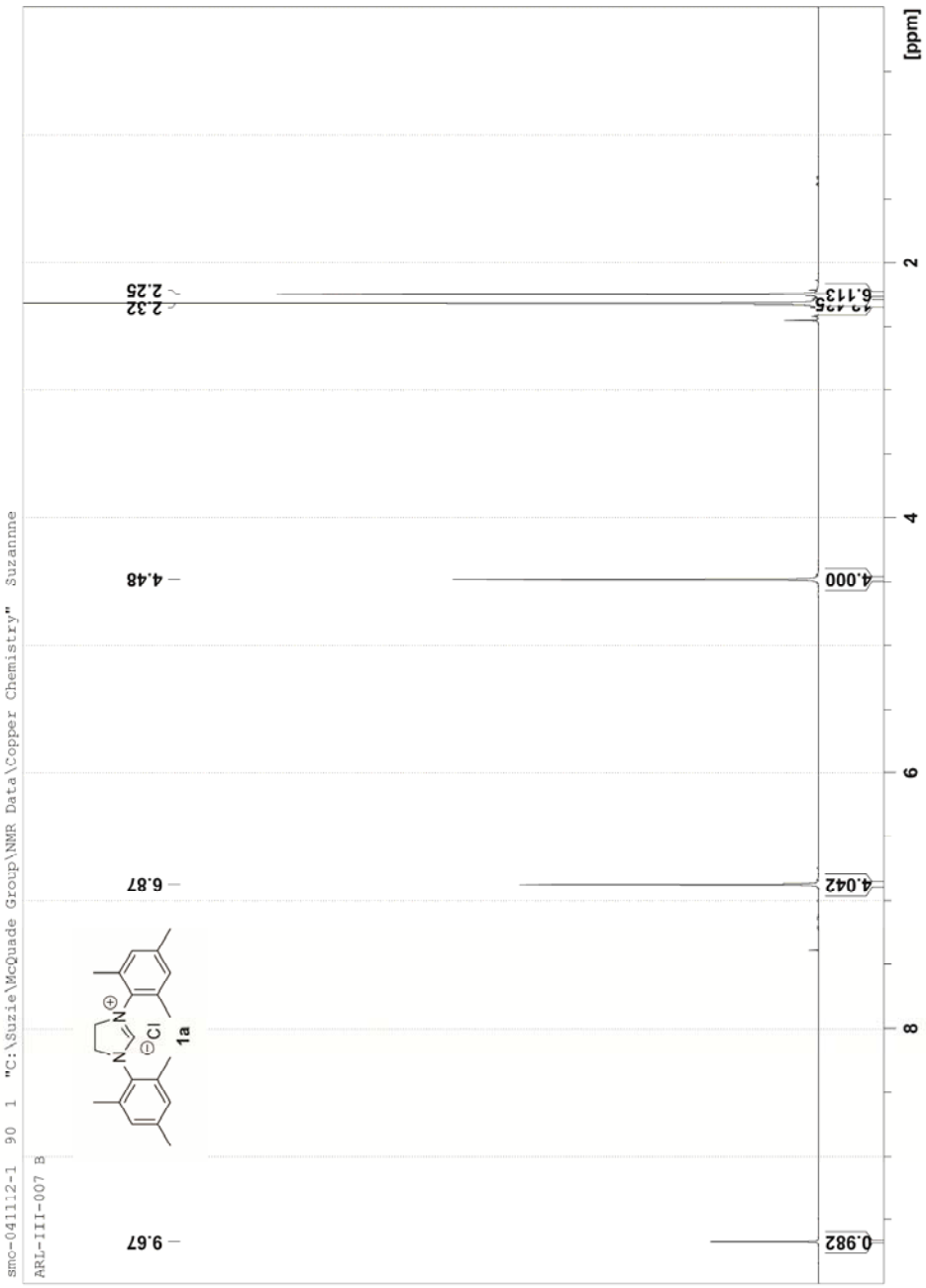

Crude reaction mixture for 3b alone going through the L-proline packed bed column
smo-vii-163
crude
[rel]
[ppm]
4.2 to 3.5 ppm
Product (5a')
Crude

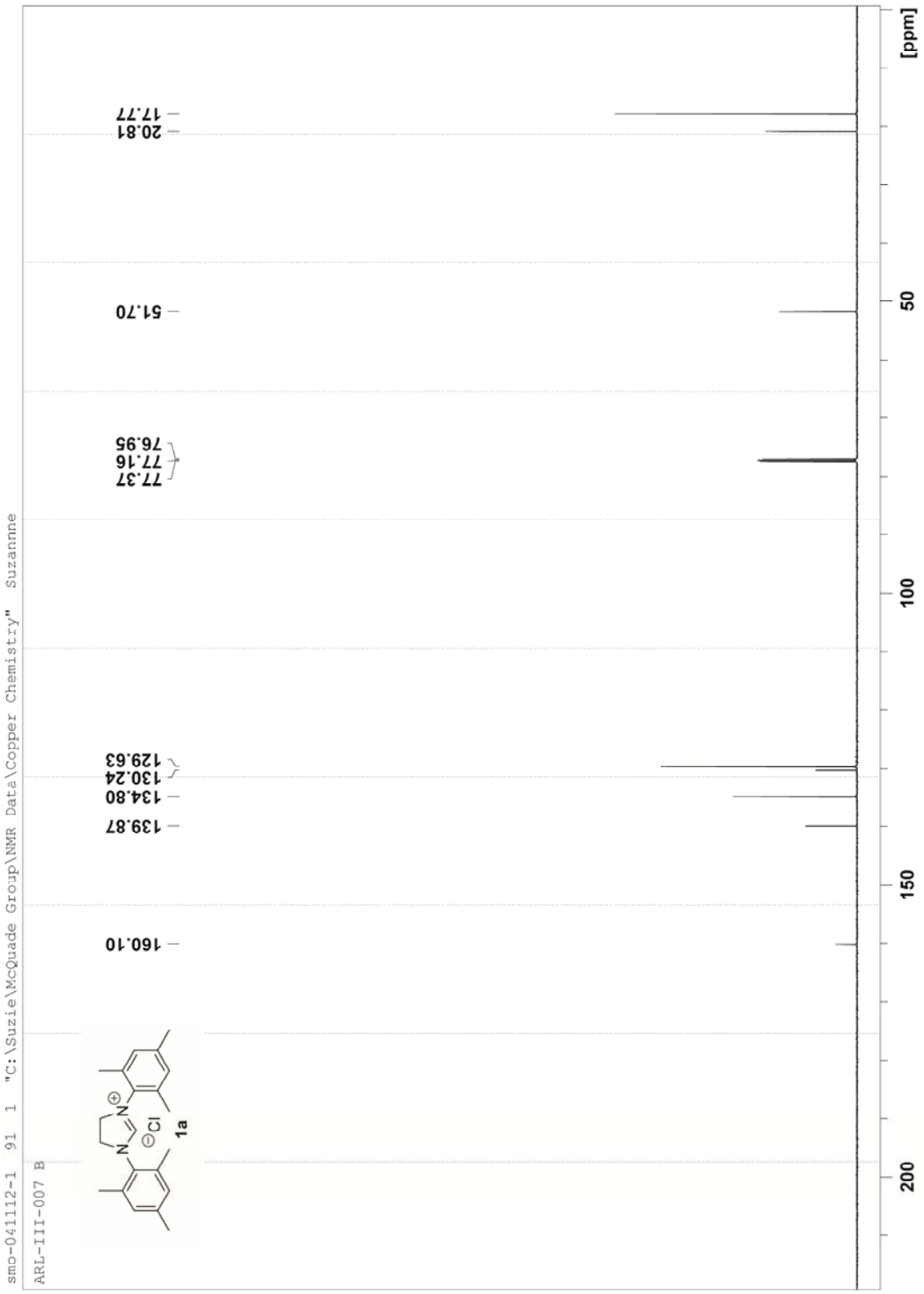

Crude reaction mixture with no 3b present
smo-vii-171 crude
[rel]
[ppm]
4.2 to 3.6 ppm
Product (5a')
Crude

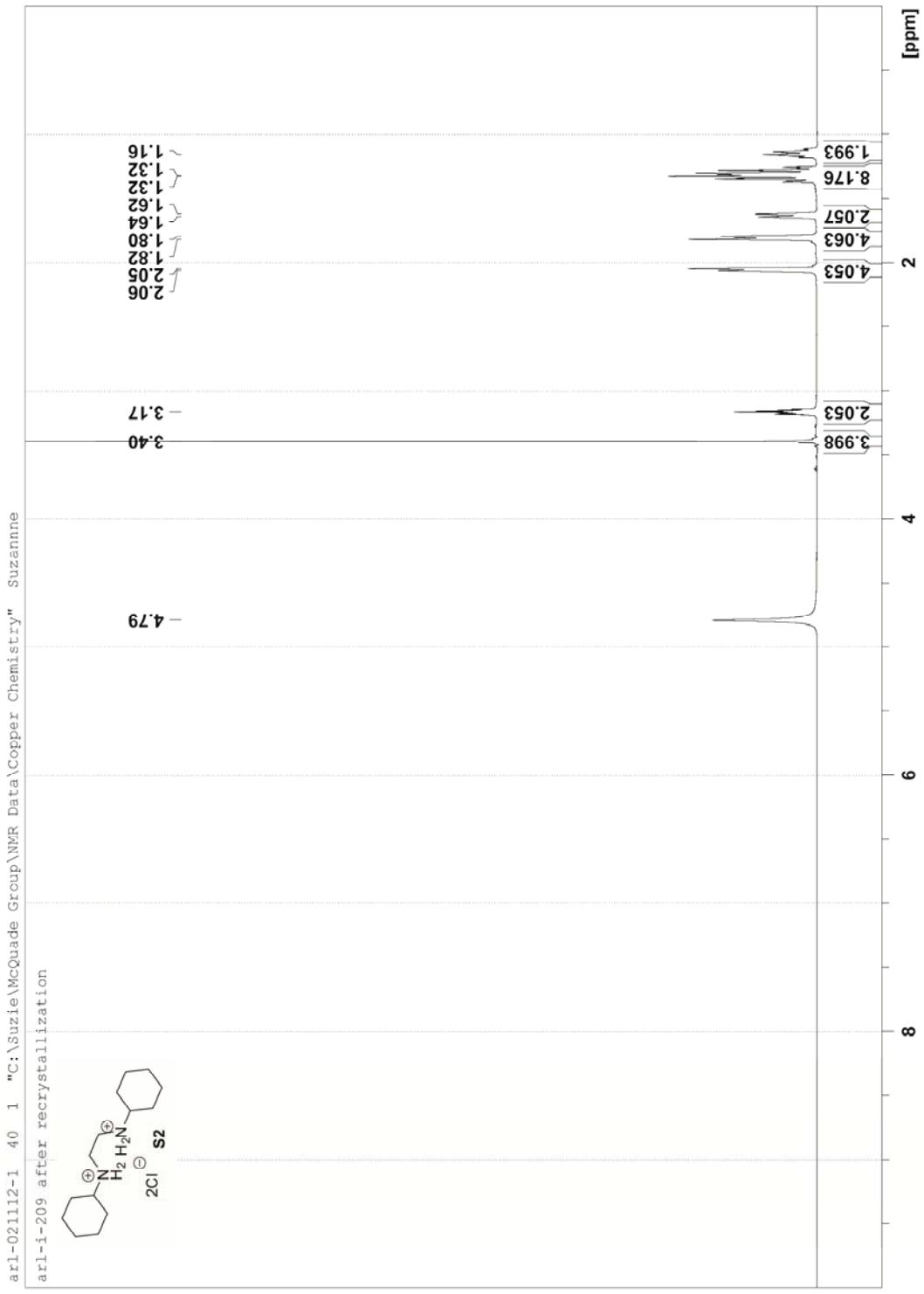
APPENDIX 3

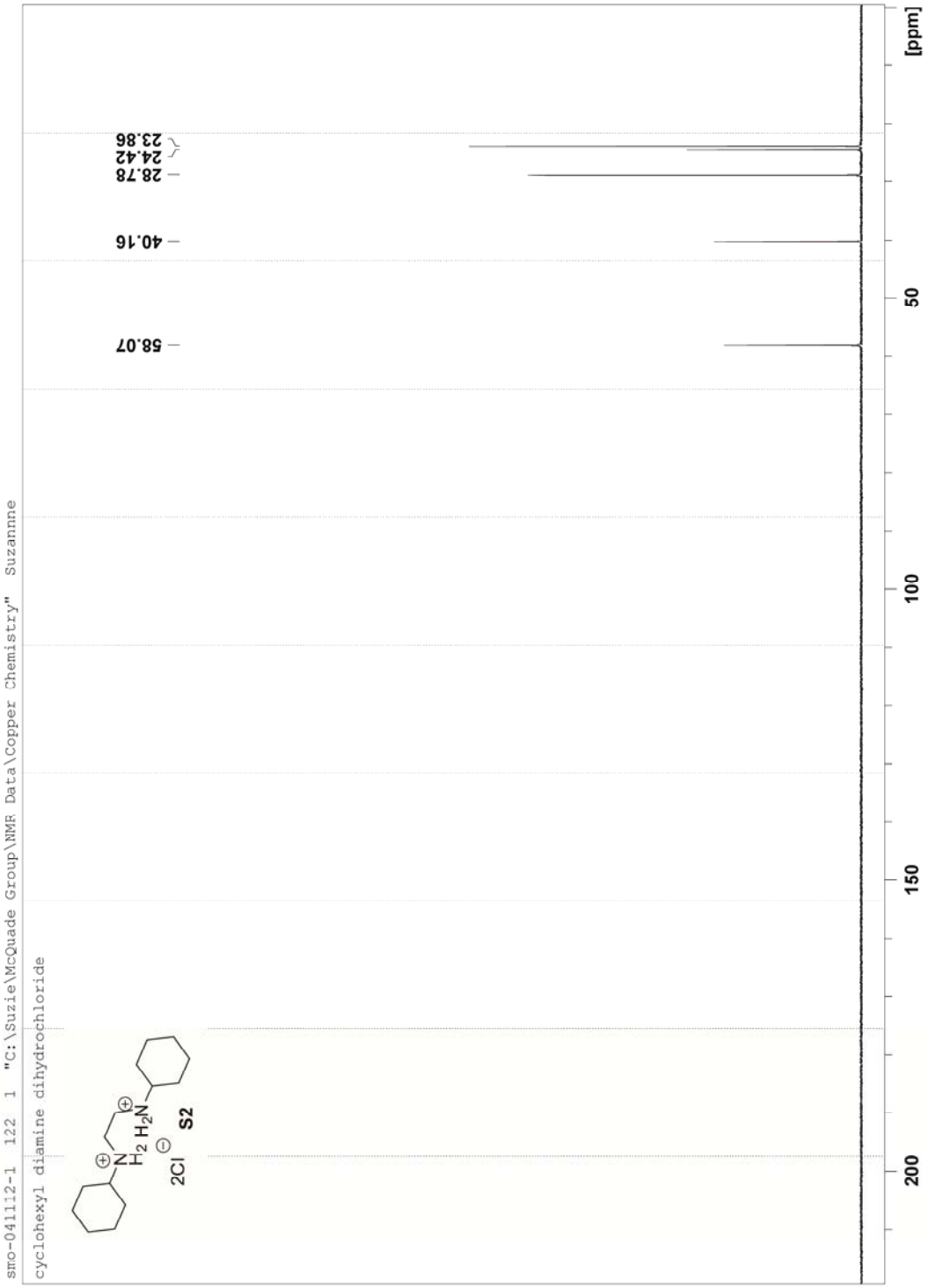
Supporting Information for Chapter 4

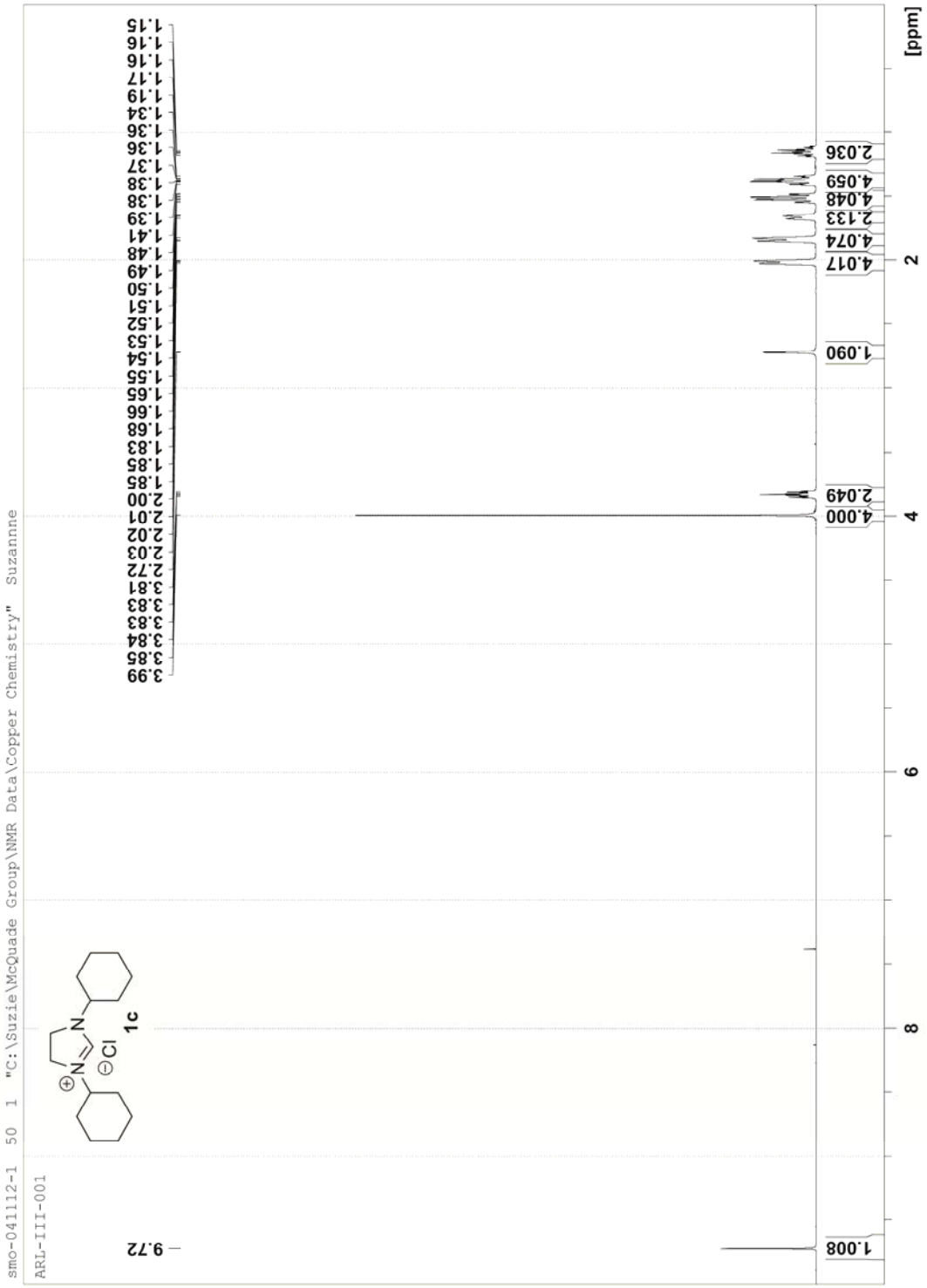
1. ^{1}H and ^{13}C NMR Spectra of Chemical Compound

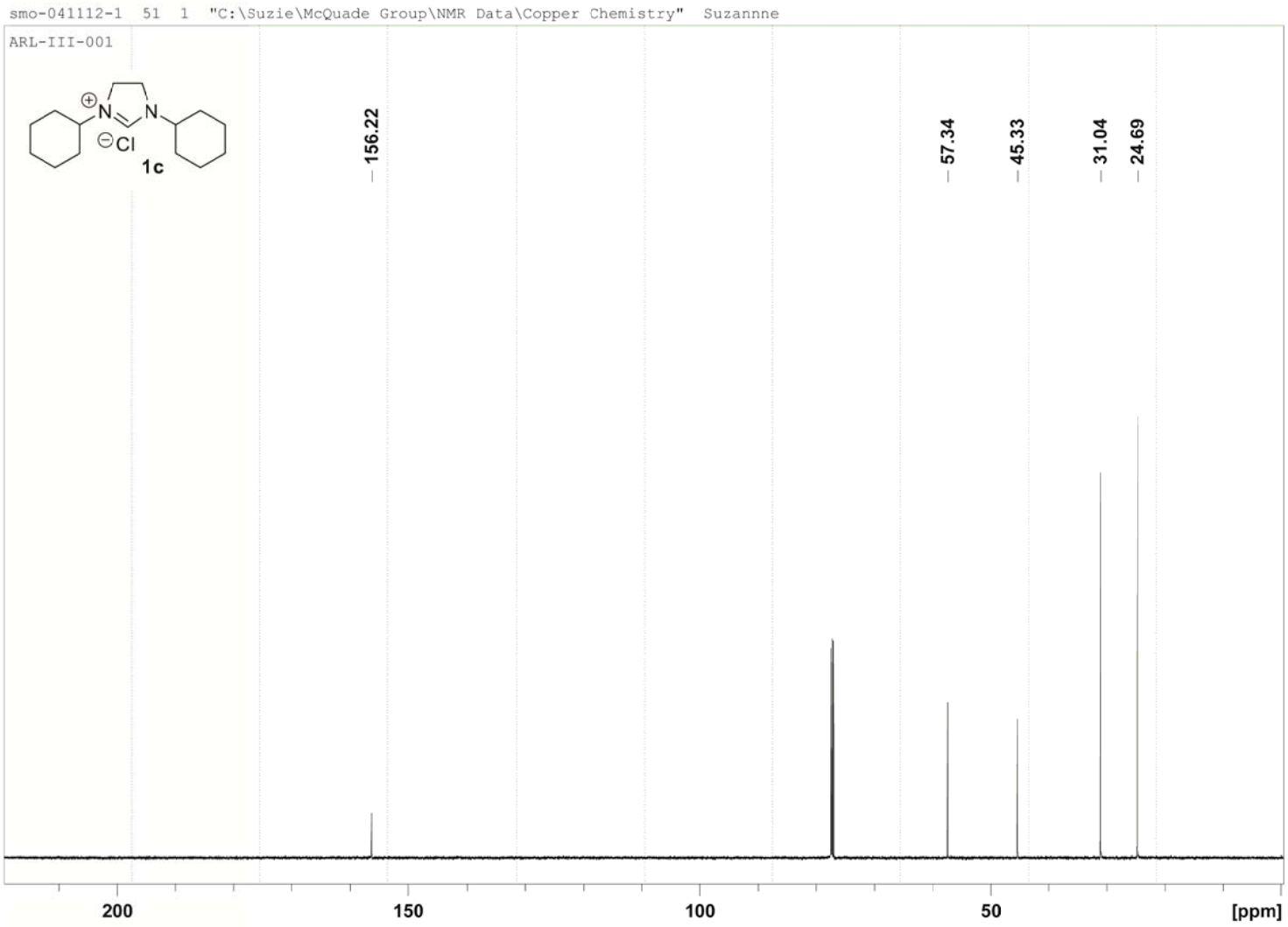


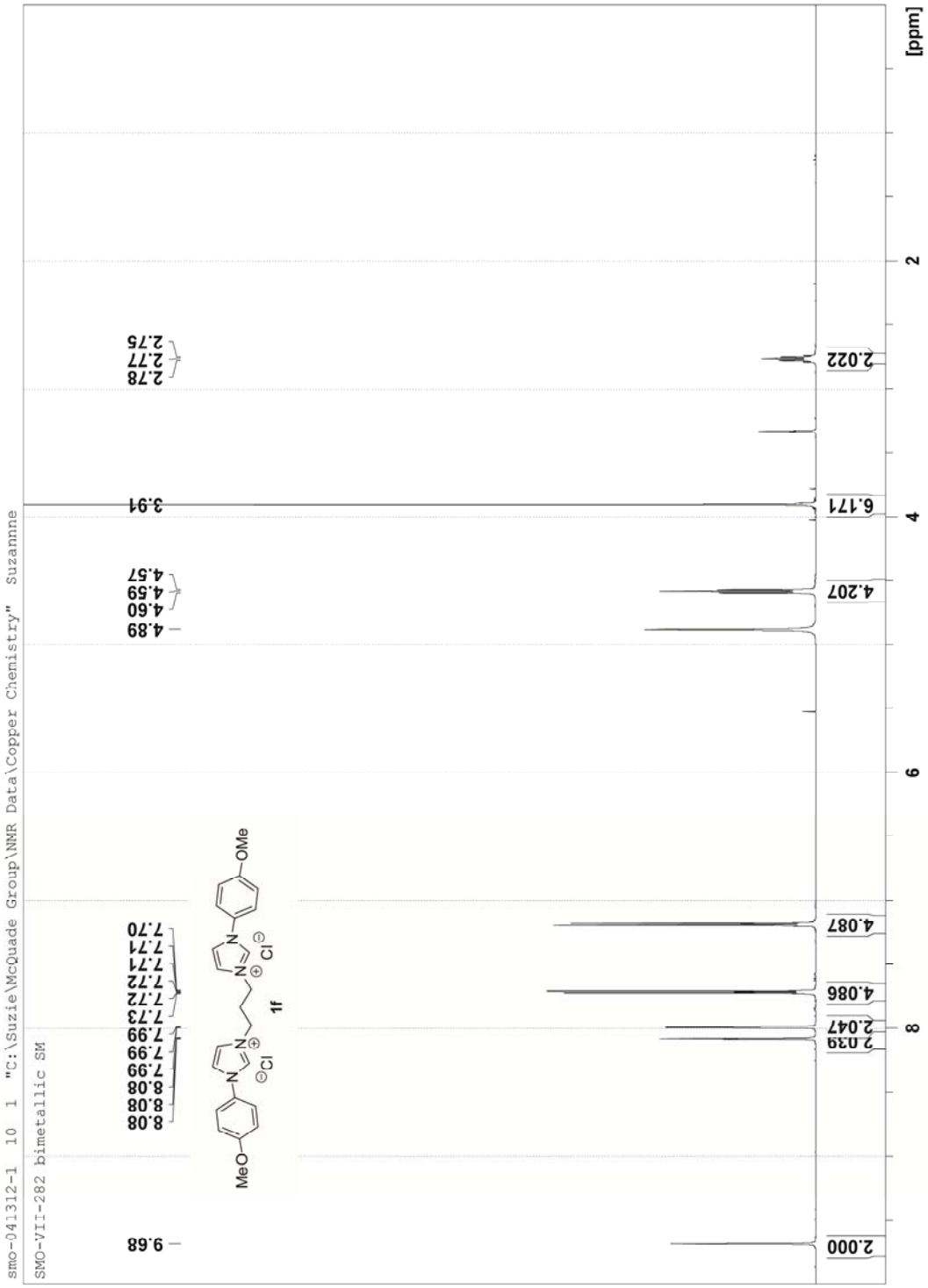

smo-041112-1 91 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne
ARL-III-007 B
1a
160.10
139.87
134.80
130.24
129.63
77.37
77.16
76.95
51.70
20.81
17.77
200
150
100
50
[ppm]

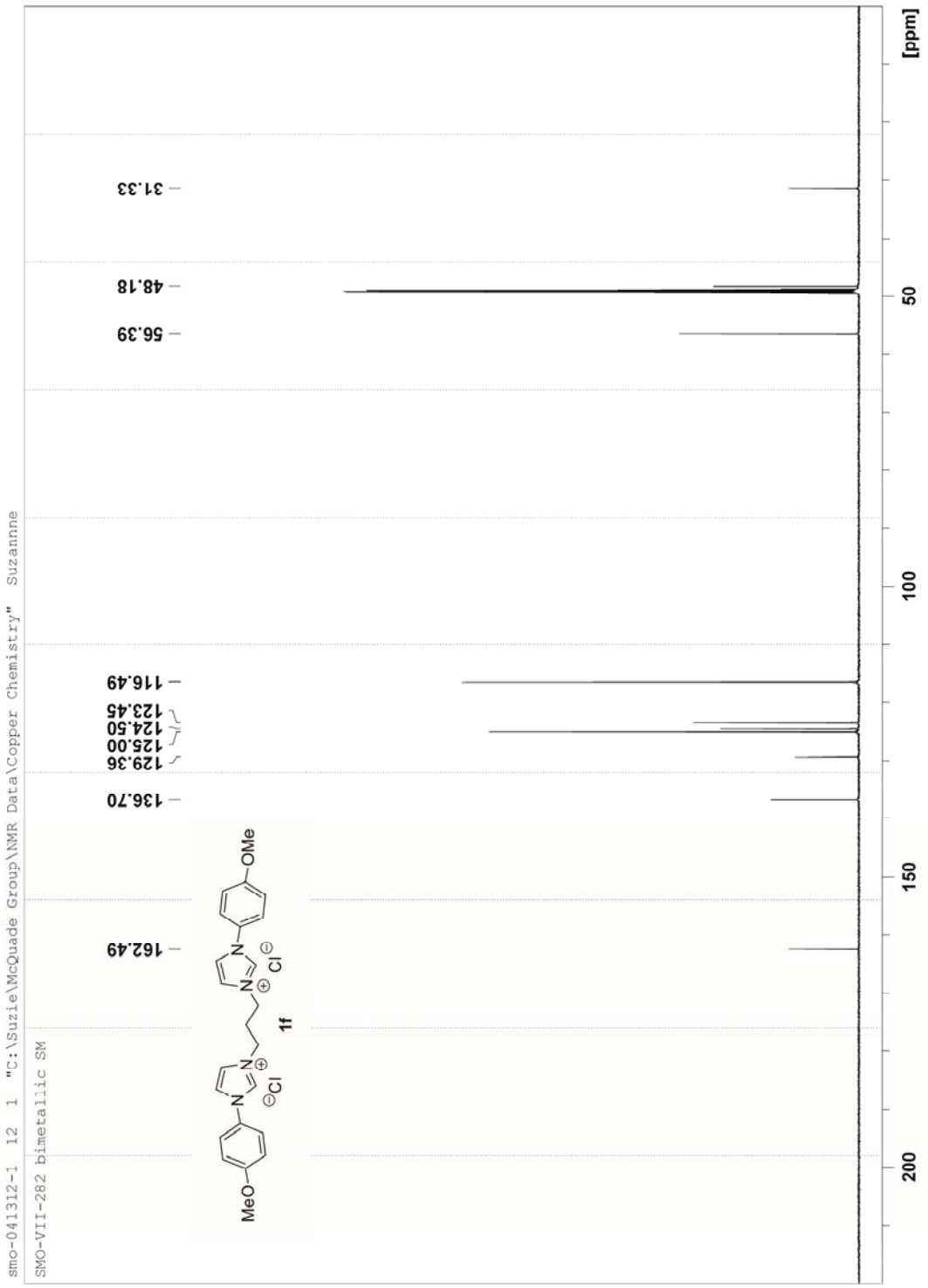

arl-021112-1 40 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
arl-i-209 after recrystallization
S2
2Cl
4.79
3.40
3.17
2.06
2.05
1.82
1.80
1.64
1.62
1.32
1.32
1.16
3.998
2.053
4.053
2.057
4.063
8.176
1.993
[ppm]

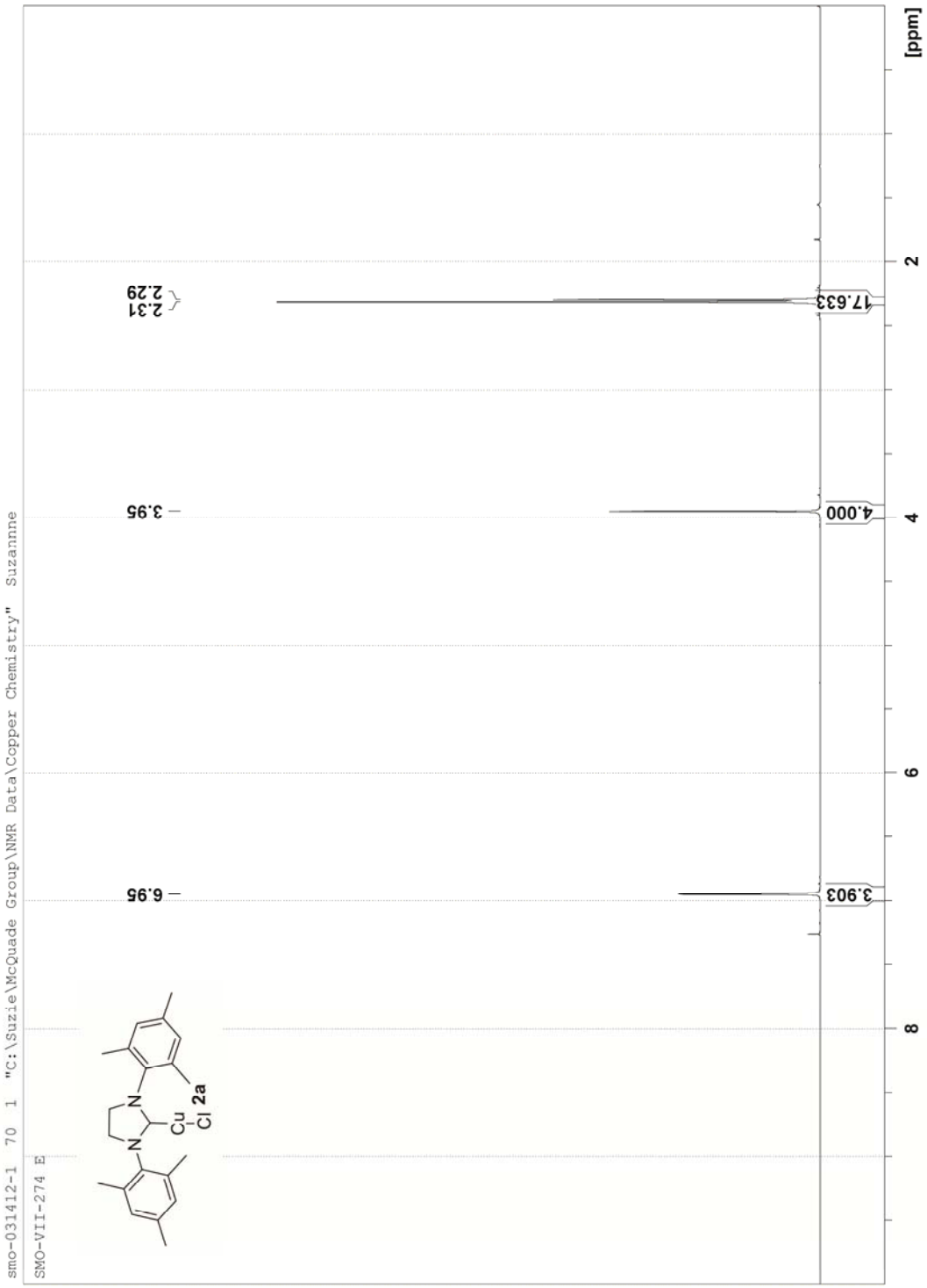

smo-041112-1 122 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
cyclohexyl diamine dihydrochloride
S2
2Cl
58.07
40.16
28.78
24.42
23.86
200
150
100
50
[ppm]

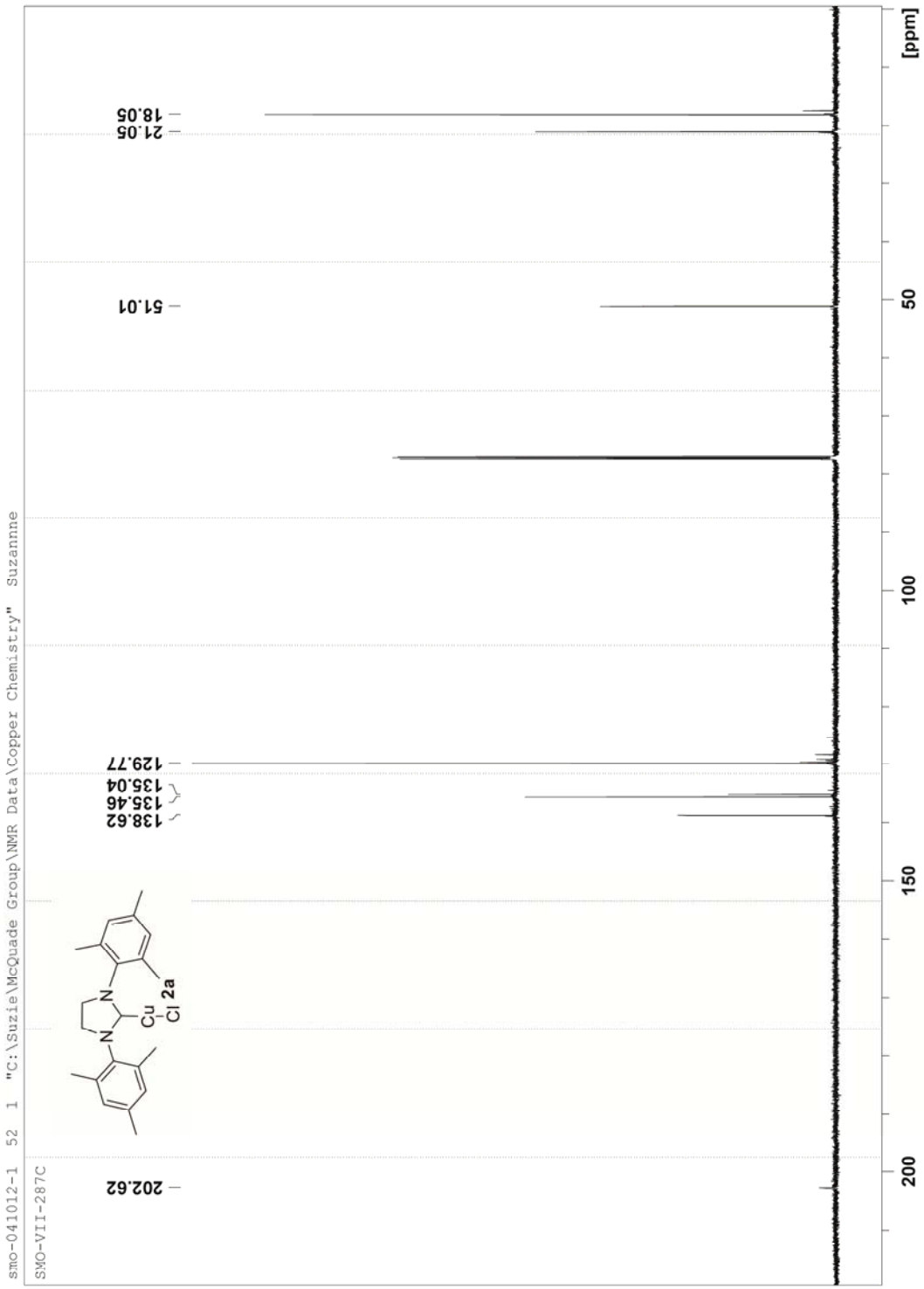

smo-041112-1 50 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
ARL-III-001
1c
9.72
3.99
3.85
3.84
3.83
3.83
3.81
3.72
2.03
2.02
2.01
2.00
1.85
1.85
1.68
1.66
1.65
1.55
1.54
1.53
1.52
1.51
1.50
1.49
1.48
1.41
1.39
1.38
1.38
1.37
1.36
1.36
1.34
1.19
1.17
1.16
1.16
1.15
1.008
4.000
2.049
1.090
4.017
4.074
2.133
4.048
4.059
2.036
8
6
4
2
[ppm]

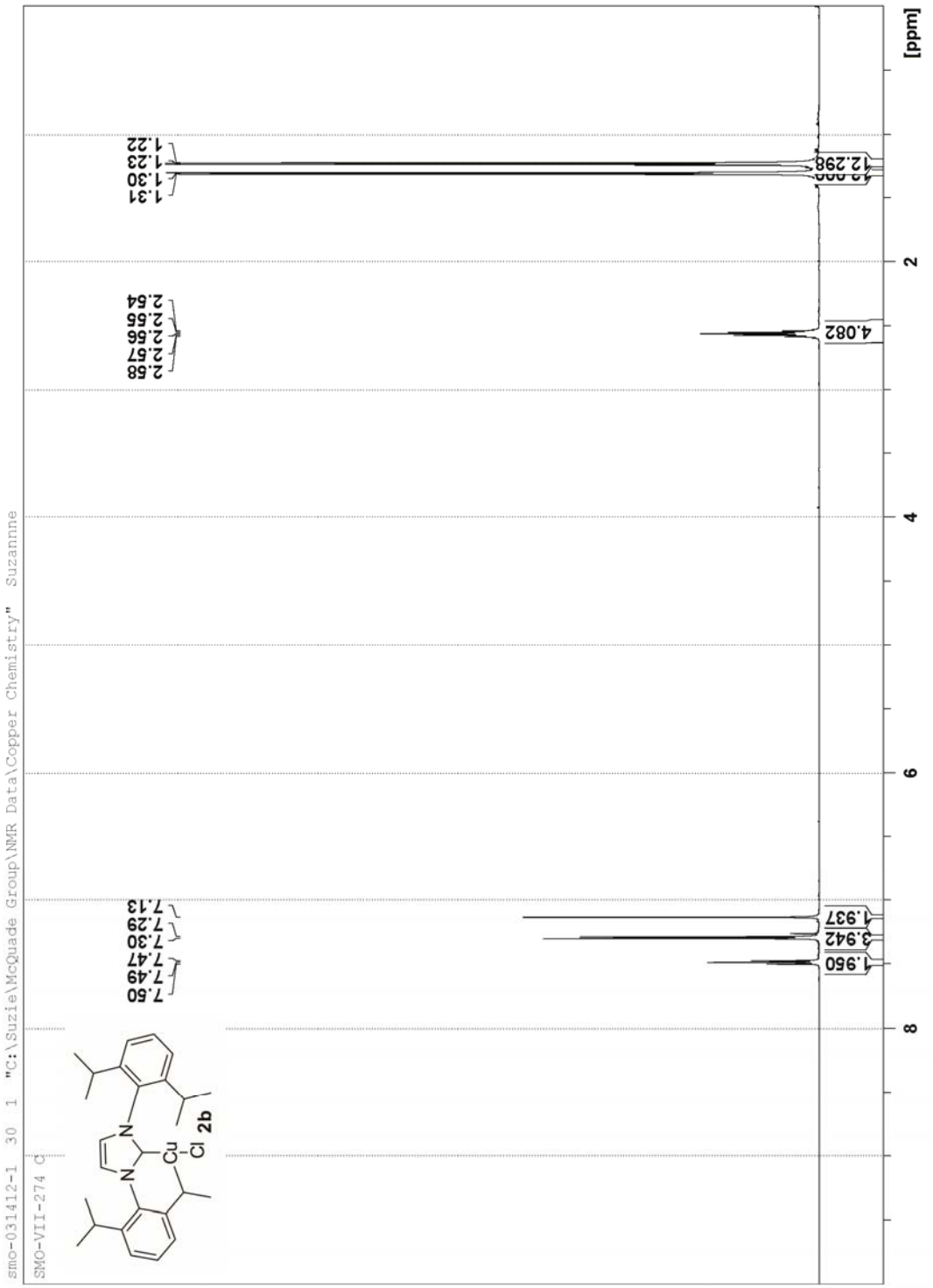

smo-041112-1 51 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
ARL-III-001
1c
156.22
57.34
45.33
31.04
24.69
200
150
100
50
[ppm]

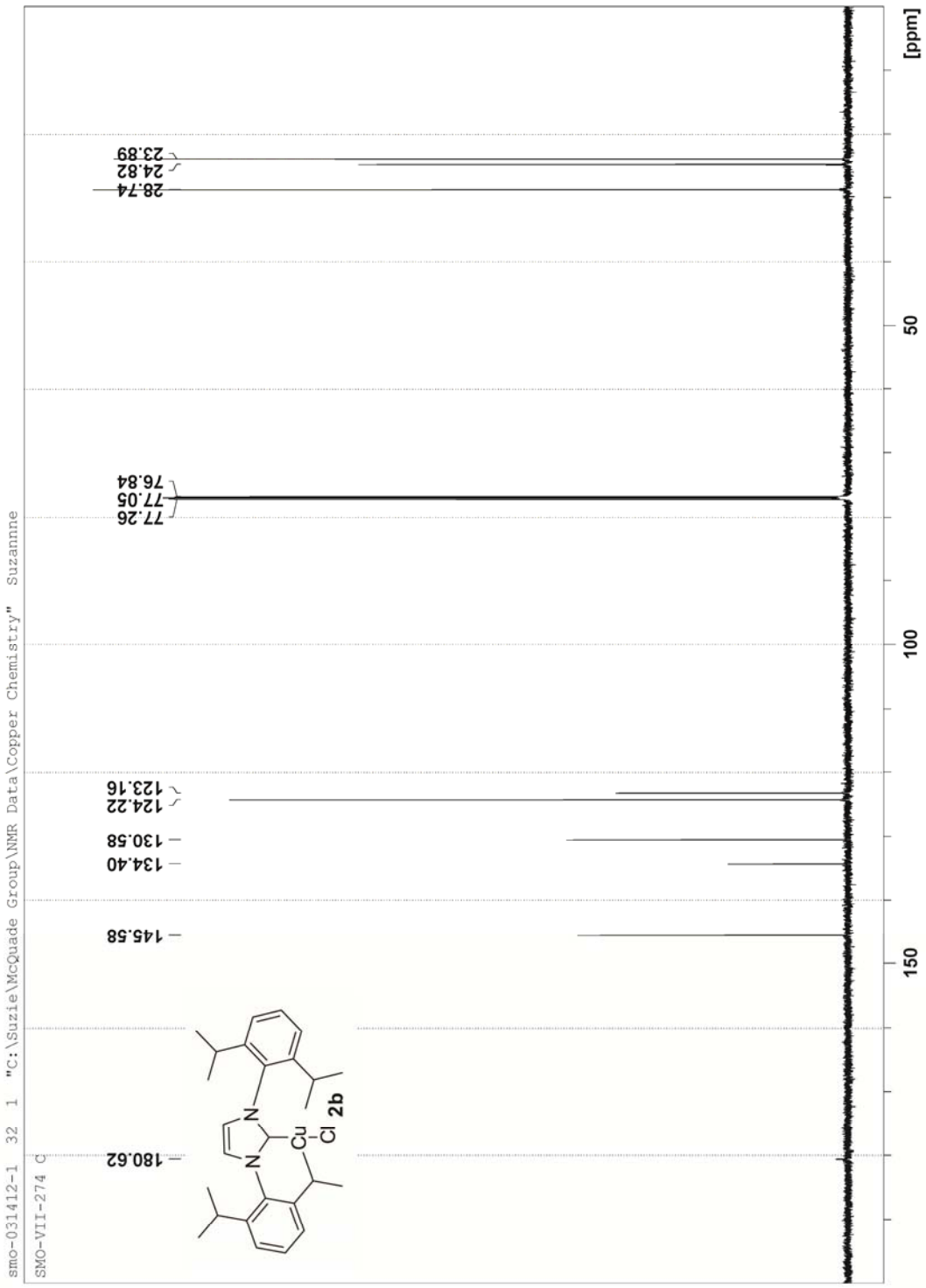

smo-041312-1 10 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-282 bimetallic SM
9.68
8.08
8.08
8.08
7.99
7.99
7.99
7.99
7.73
7.72
7.72
7.71
7.71
7.70
4.89
4.60
4.59
4.57
3.91
2.78
2.77
2.75
MeO
OMe
Cl
1f
2.000
4.087
4.086
2.047
2.039
4.207
6.171
2.022
[ppm]

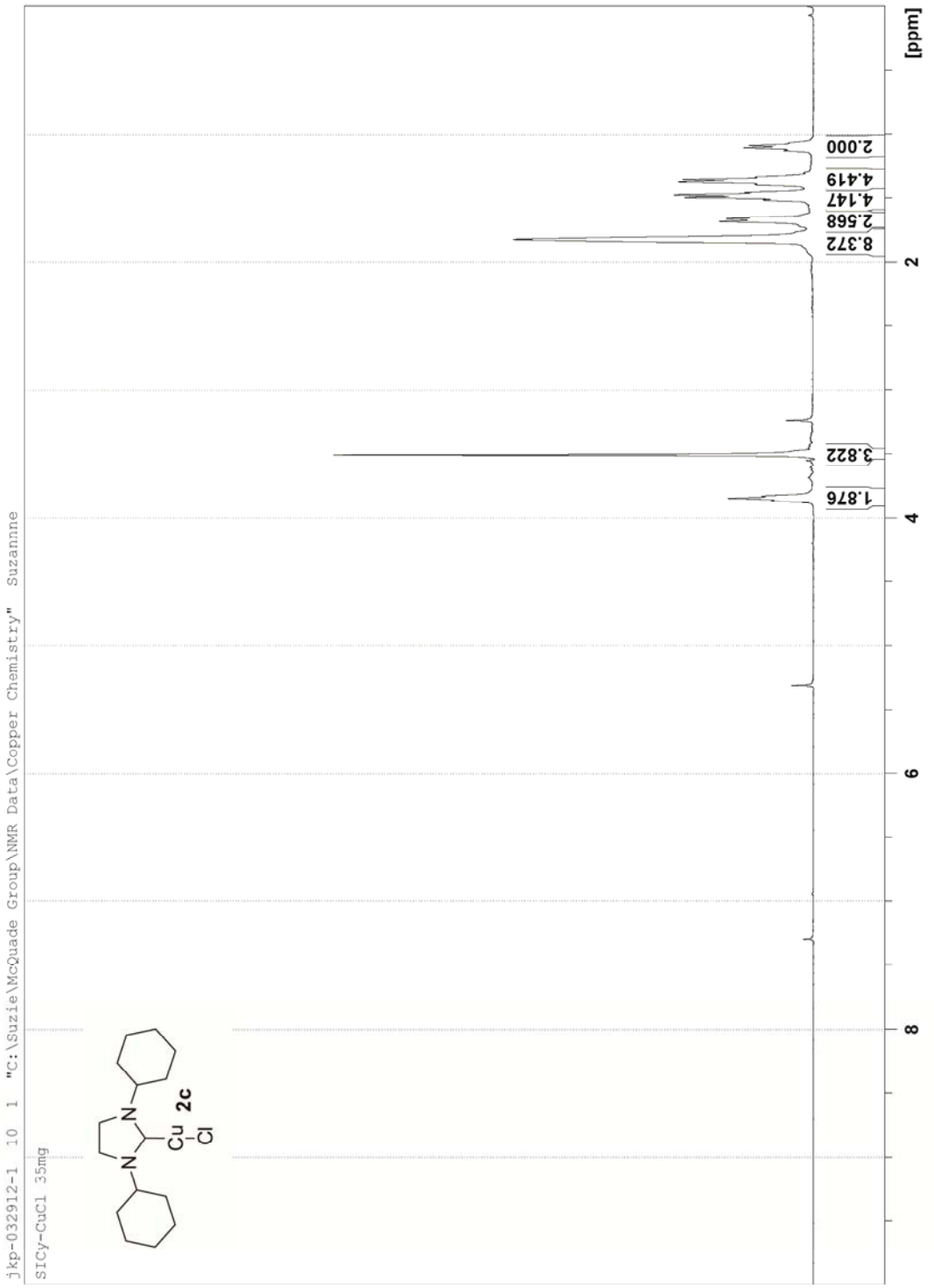

smo-041312-1 12 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-282 bimetallic SM
162.49
136.70
129.36
125.00
124.50
123.45
116.49
56.39
48.18
31.33
200
150
100
50
[ppm]
MeO
OMe
1f

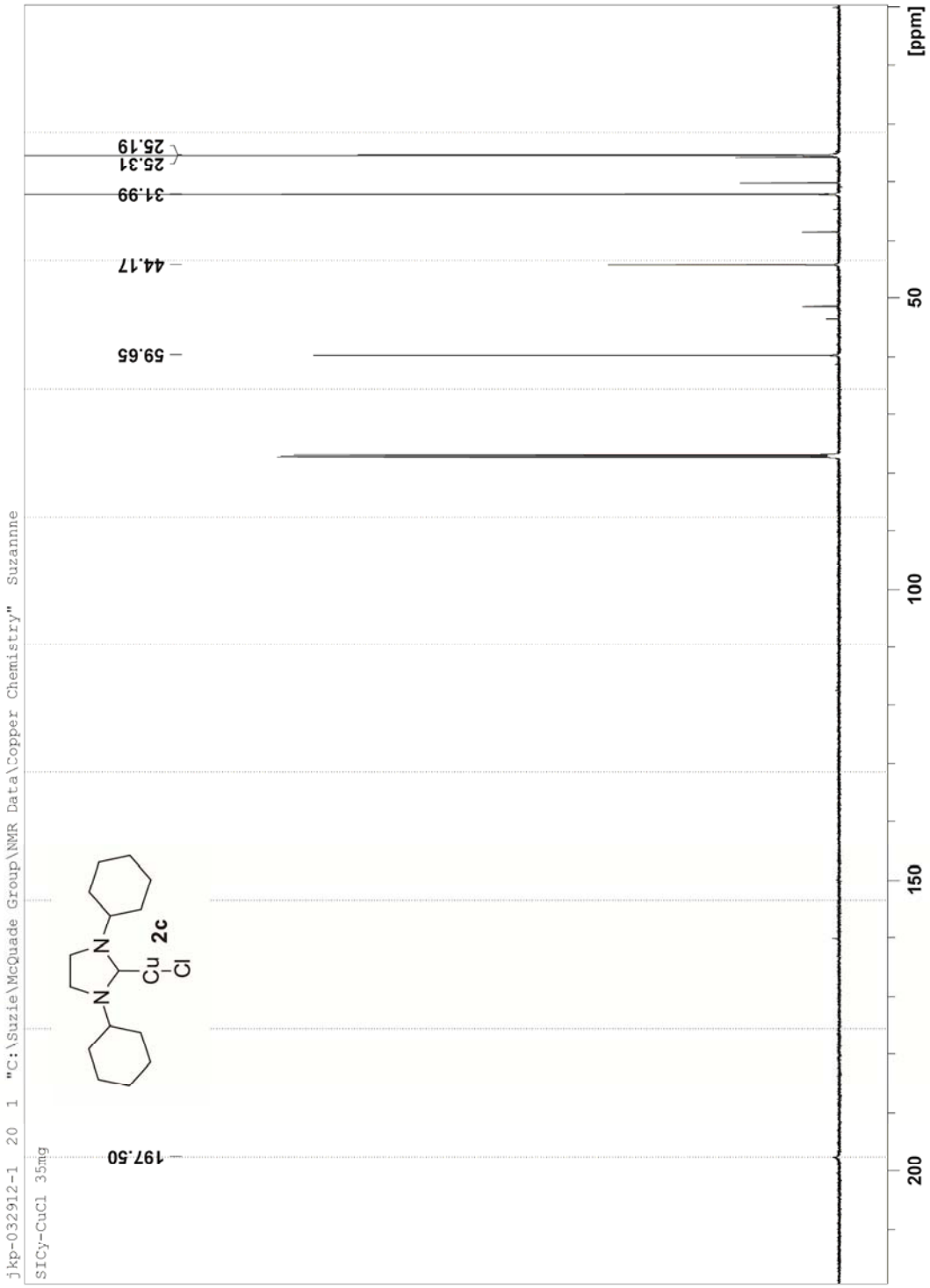

smo-031412-1 70 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-274 E
2a
Cu
Cl
N
N
6.95
3.95
2.31
2.29
3.903
4.000
17.633
8
6
4
2
[ppm]

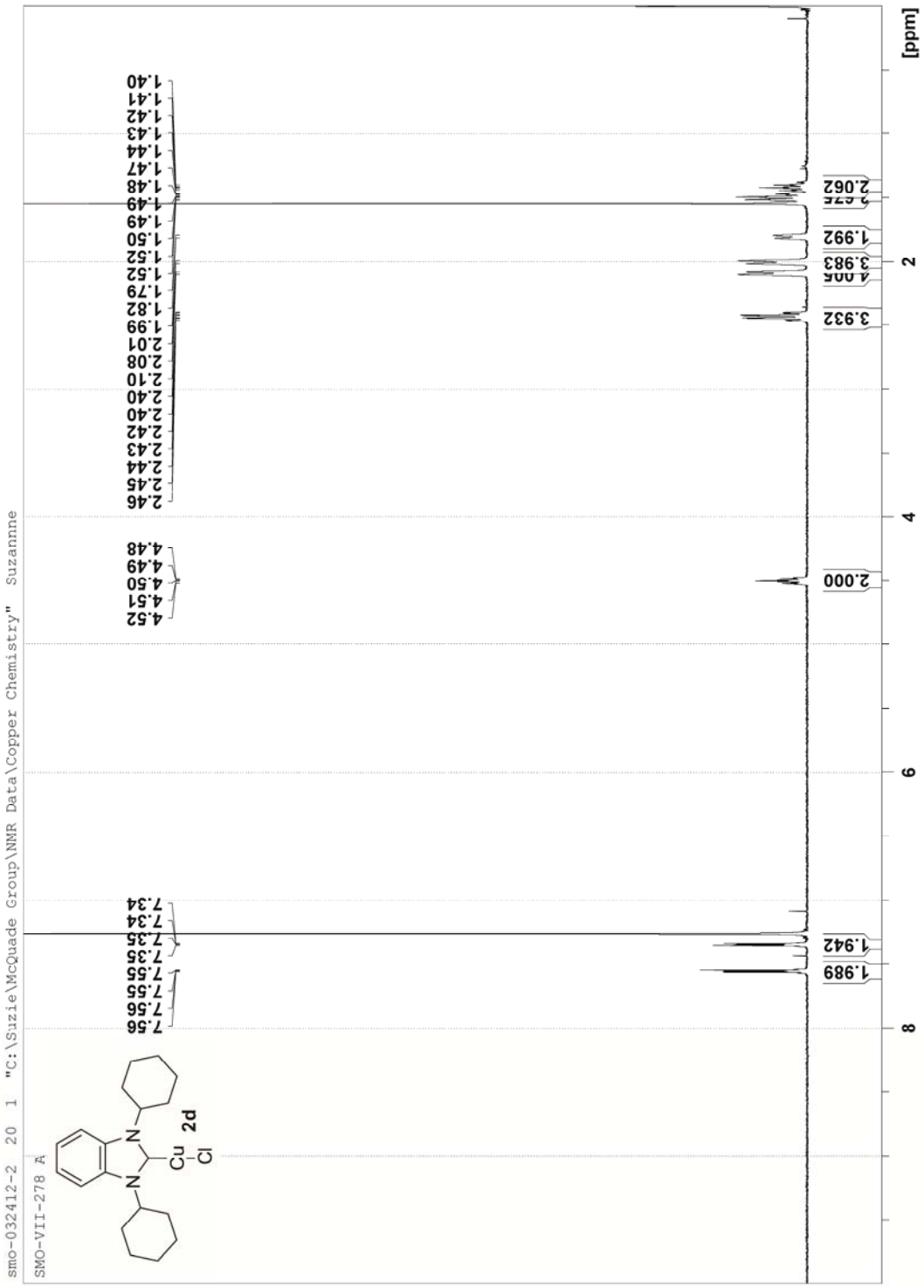

smo-041012-1 52 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne
SMO-VII-287C
202.62
138.62
135.46
135.04
129.77
51.01
21.05
18.05
Cu
Cl
Cl
2a
200
150
100
50
[ppm]


smo-031412-1 30 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-274 C
2b
Cu
Cl
N
N
7.60
7.49
7.47
7.30
7.29
7.13
2.68
2.67
2.66
2.66
2.55
2.54
1.31
1.30
1.23
1.22
1.960
3.942
1.937
4.082
12.298
[ppm]
8
6
4
2


smo-031412-1 32 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-274 C
180.62
145.58
134.40
130.58
124.22
123.16
77.26
77.05
76.84
28.74
24.82
23.89
N
N
Cu
Cl
2b
150
100
50
[ppm]


jkp-032912-1 10 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SICy-CuCl 35mg
2c
1.876
3.822
8.372
2.568
4.147
4.419
2.000
8
6
4
2
[ppm]


jkp-032912-1 20 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SICy-CuCl 35mg
197.50
59.65
44.17
31.99
25.31
25.19
N
N
Cu
Cl
2c
200
150
100
50
[ppm]


smo-032412-2 20 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-278 A
2d
Cu
Cl
N
N
7.56
7.56
7.55
7.55
7.35
7.35
7.34
7.34
7.34
4.52
4.51
4.50
4.49
4.48
2.46
2.45
2.44
2.43
2.42
2.40
2.40
2.10
2.08
2.01
1.99
1.82
1.79
1.52
1.52
1.50
1.49
1.49
1.48
1.47
1.44
1.43
1.42
1.41
1.40
1.989
1.942
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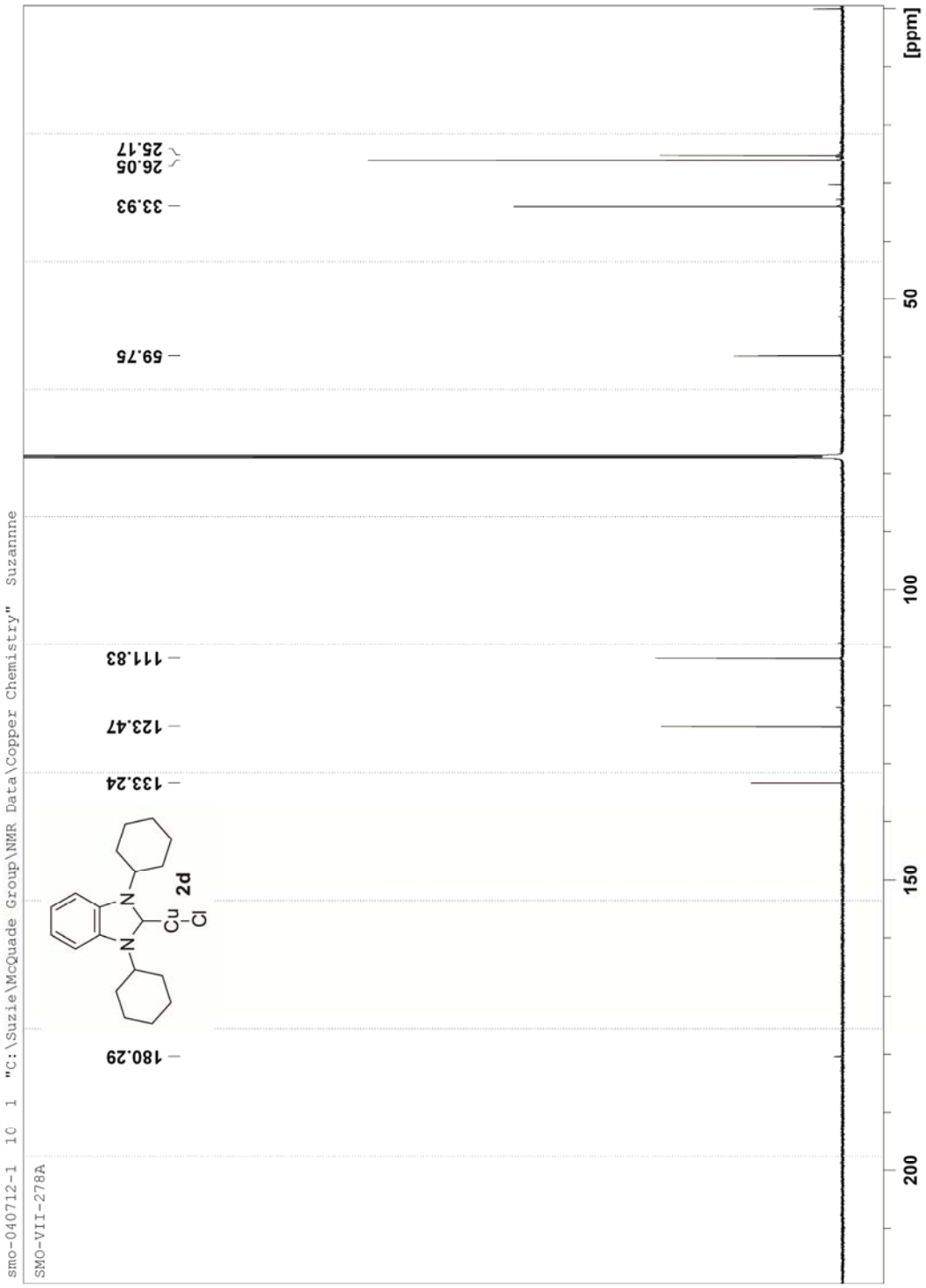
3.932
4.005
3.983
1.992
3.626
2.062
8
6
4
2
[ppm]


smo-040712-1 10 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-278A
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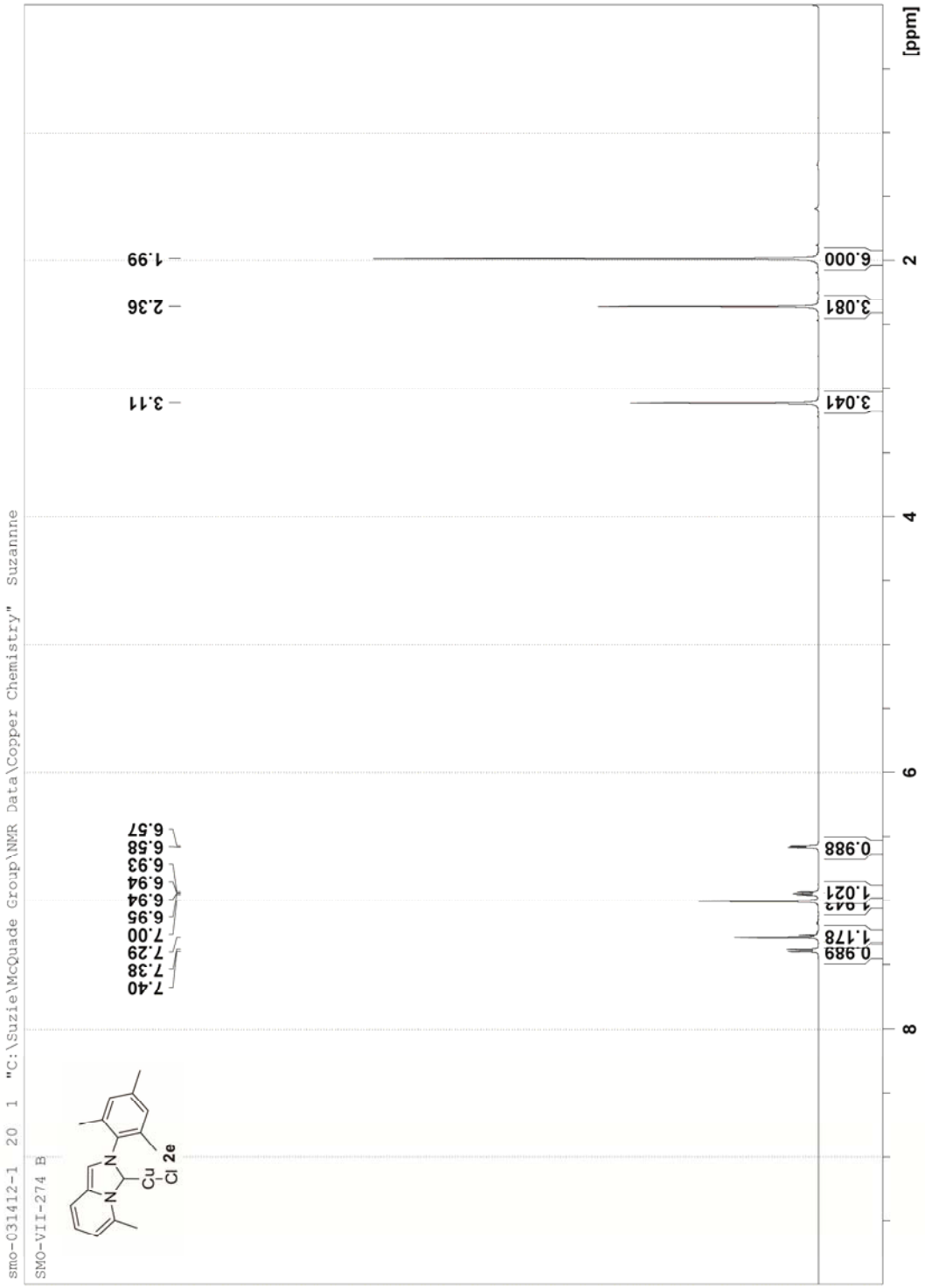
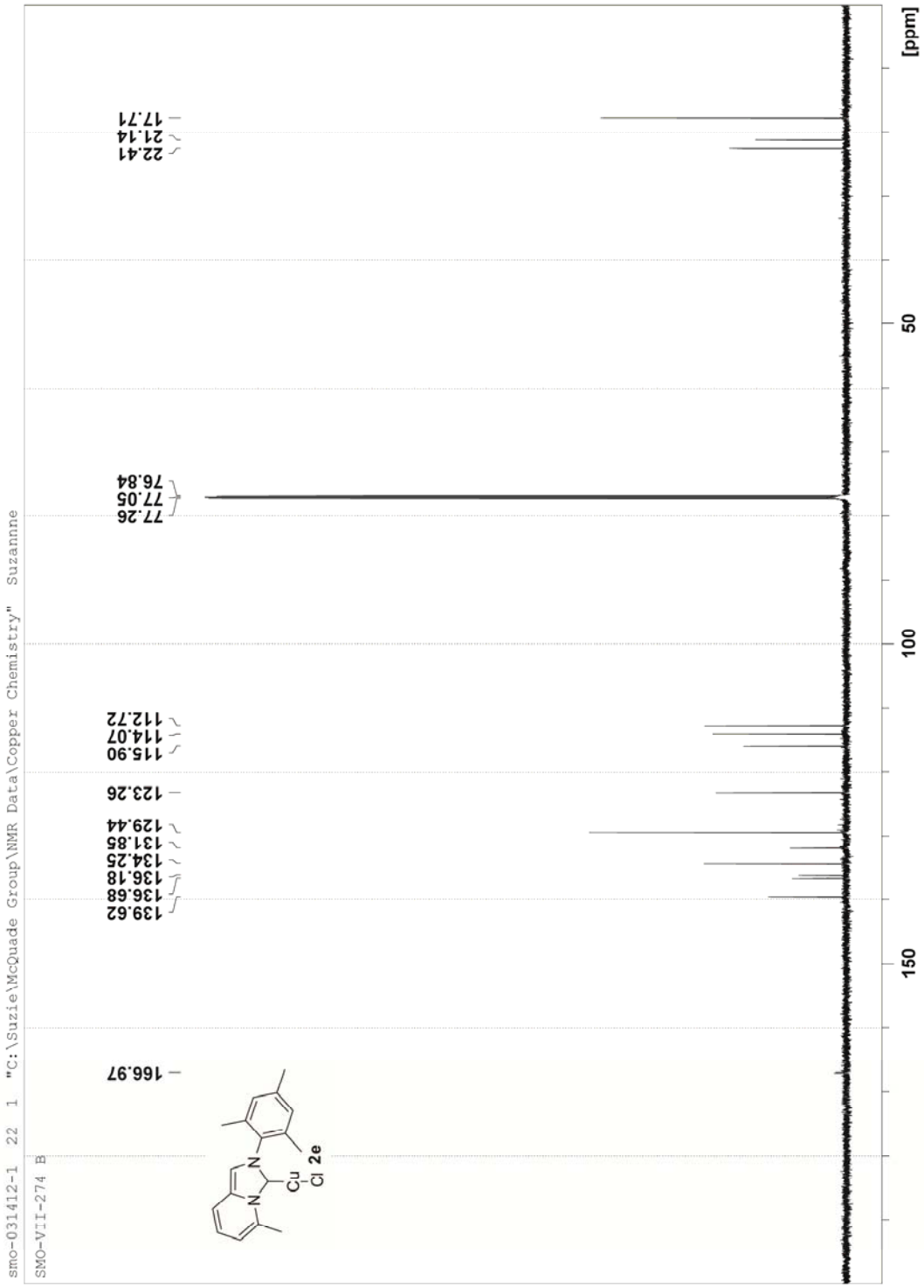
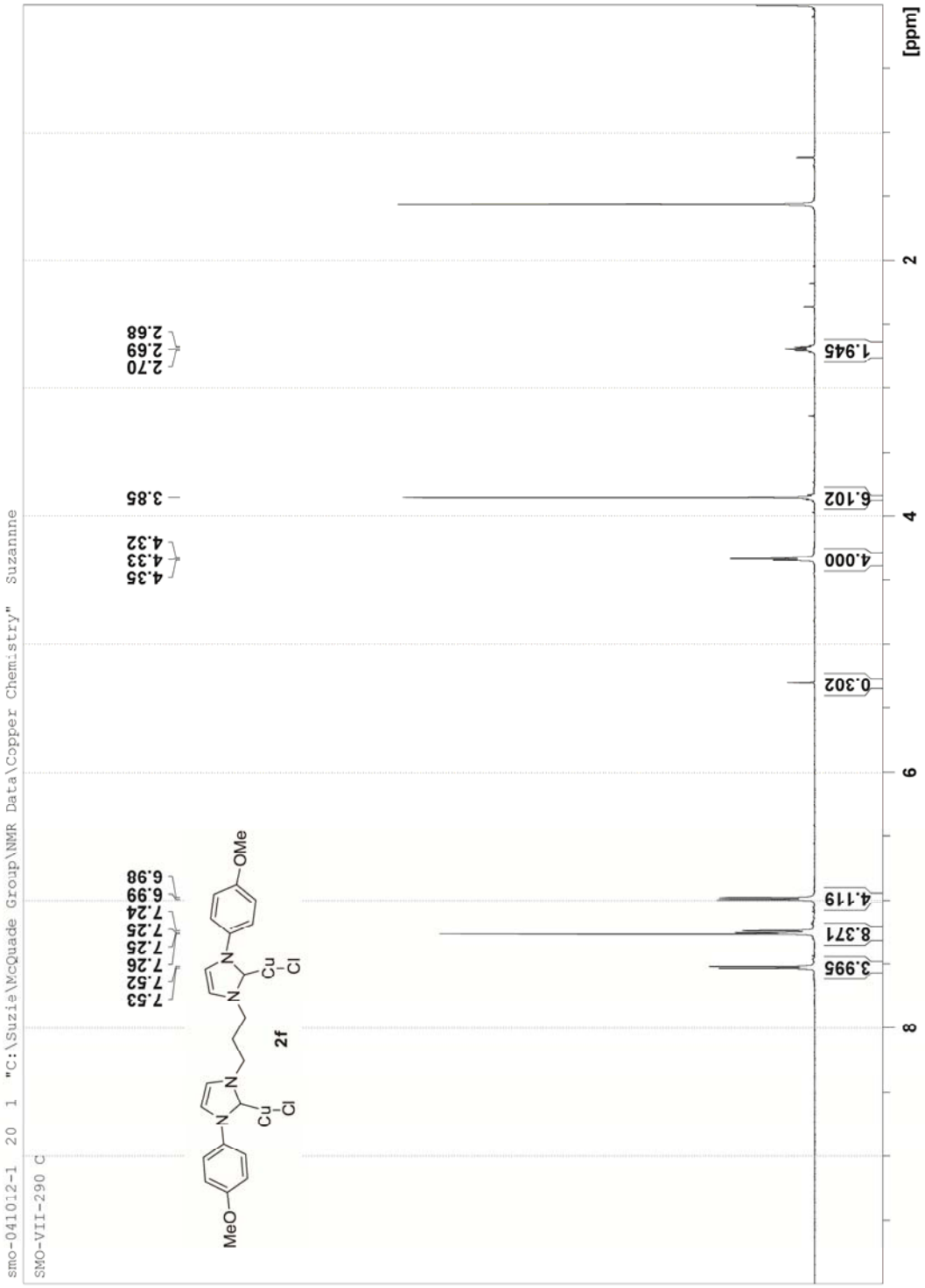
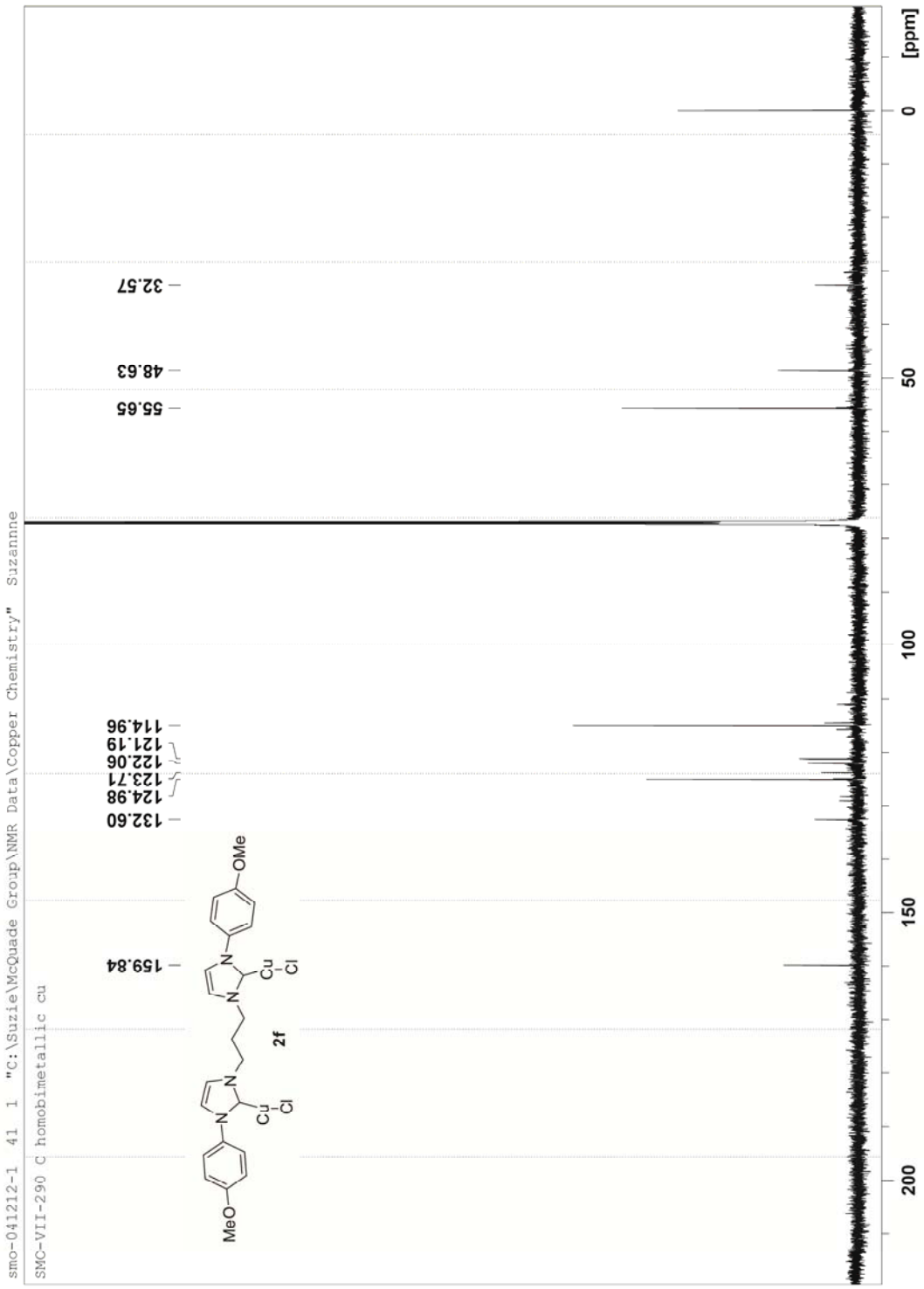
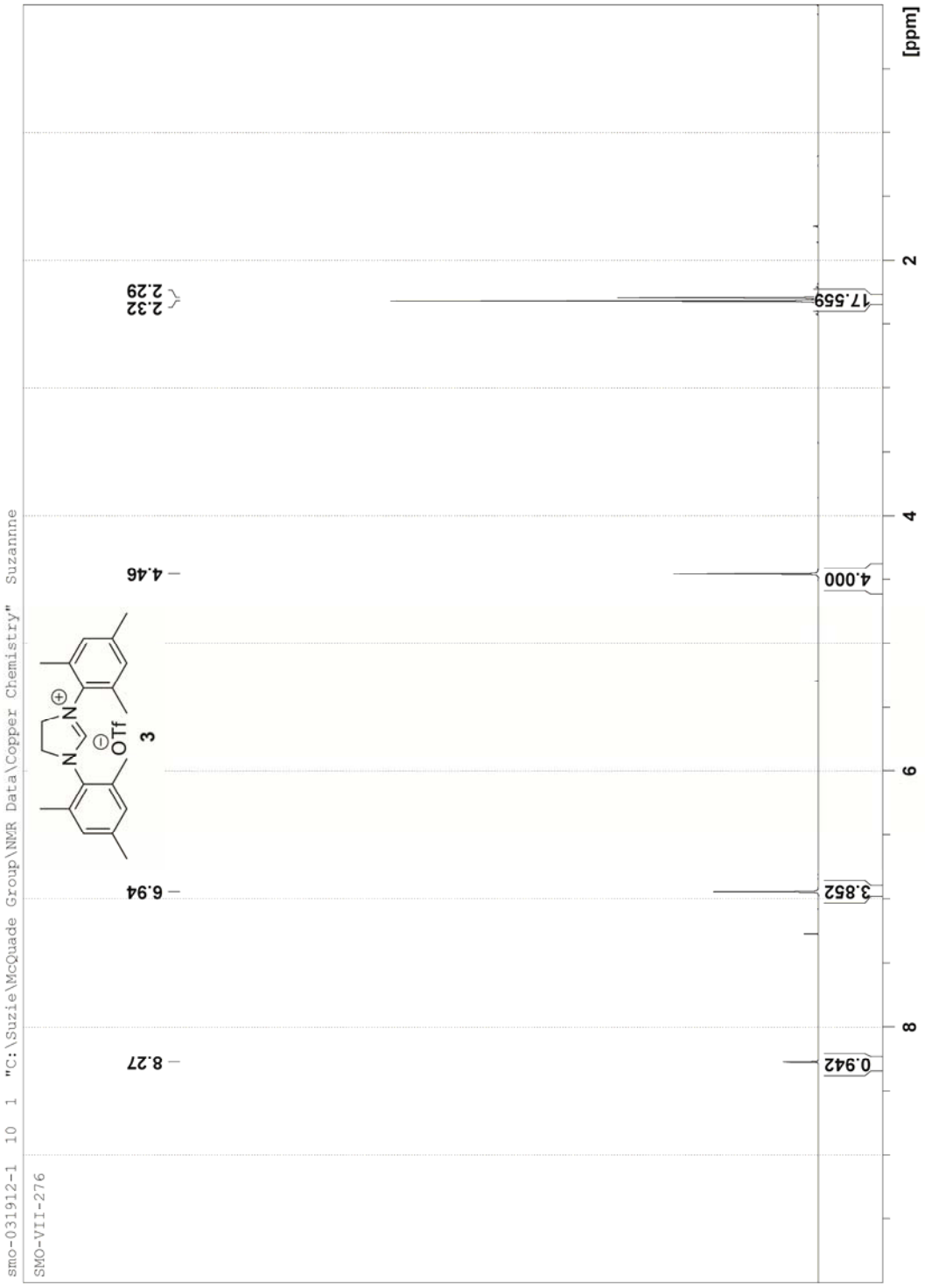
133.24
123.47
111.83
59.75
33.93
26.05
25.17
2d
[ppm]
200
150
100
50

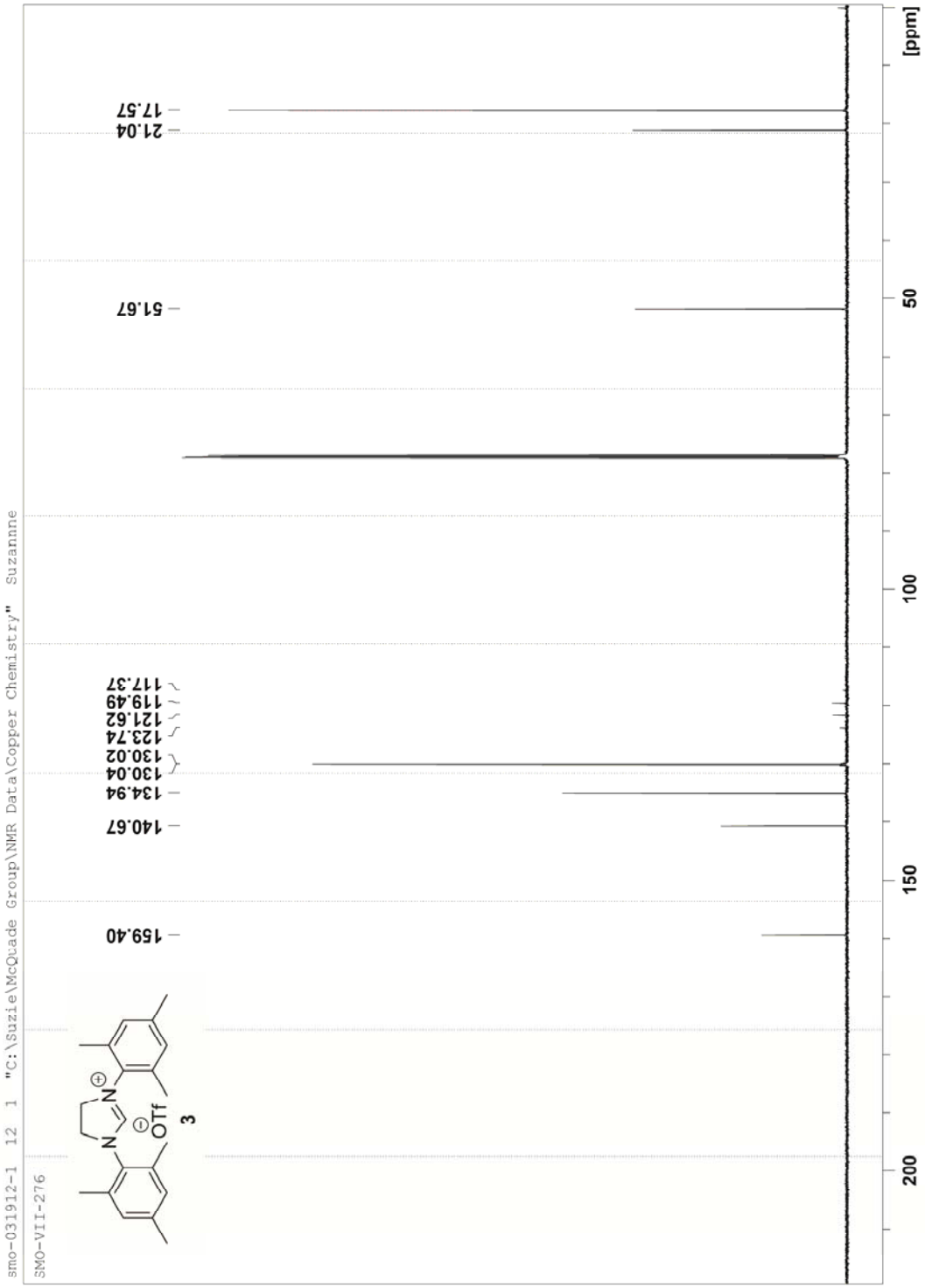

smo-031412-1 20 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-274 B
Cu
Cl
2e
7.40
7.38
7.29
7.00
6.95
6.94
6.94
6.93
6.58
6.57
3.11
2.36
1.99
0.989
1.178
1.043
1.021
0.988
3.041
3.081
6.000
8
6
4
2
[ppm]

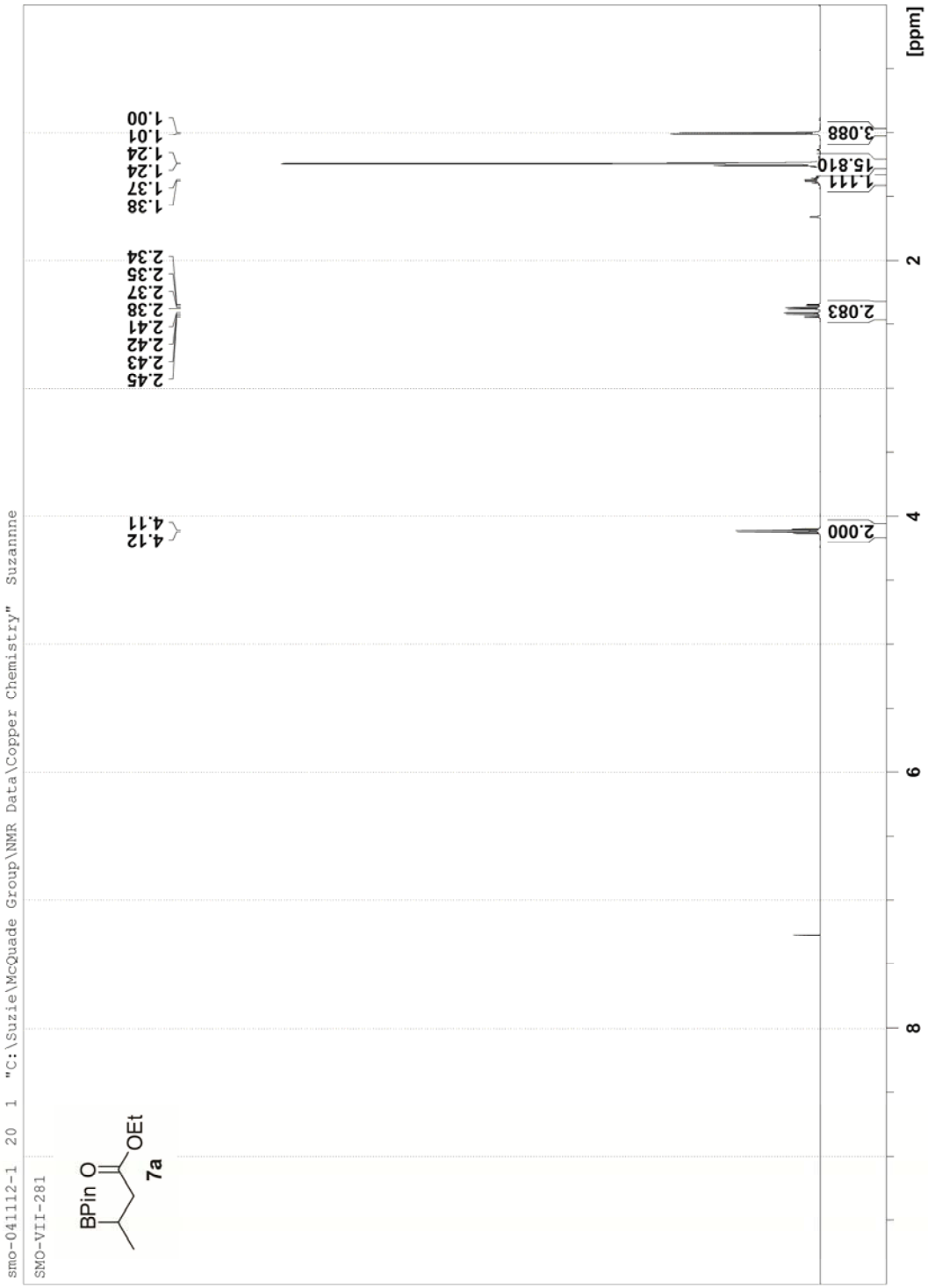

smo-031412-1 22 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-274 B
166.97
139.62
136.68
136.18
134.25
131.85
129.44
123.26
115.90
114.07
112.72
77.26
77.05
76.84
22.41
21.14
17.71
Cu
Cl
2e
150
100
50
[ppm]

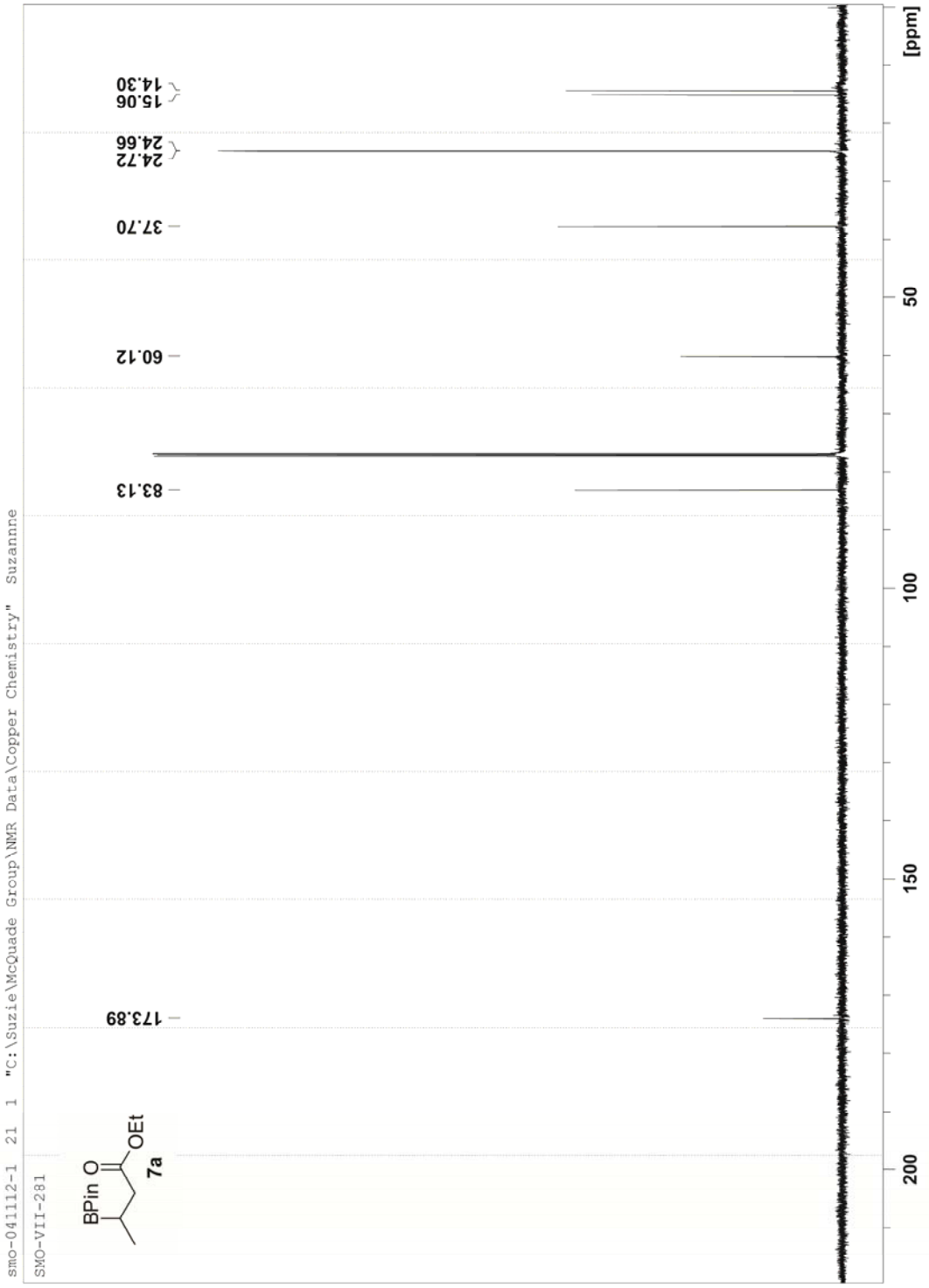

smo-041012-1 20 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-290 C
MeO
OMe
Cu
Cl
Cl
2f
7.53
7.52
7.26
7.25
7.25
7.24
6.99
6.98
4.35
4.33
4.32
3.85
2.70
2.69
2.68
3.995
8.371
4.119
0.302
4.000
6.102
1.945
8
6
4
2
[ppm]


smo-041212-1 41 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMC-VII-290 C homobimetallic cu
159.84
132.60
124.98
123.71
122.06
121.19
114.96
55.65
48.63
32.57
OMe
MeO
Cu
Cl
2f
200
150
100
50
0
[ppm]


smo-031912-1 10 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-276
8.27
6.94
4.46
2.32
2.29
0.942
3.852
4.000
17.559
OTf
3
8
6
4
2
[ppm]


smo-031912-1 12 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-276
3
OTf
159.40
140.67
134.94
130.04
130.02
123.74
121.62
119.49
117.37
51.67
21.04
17.57
200
150
100
50
[ppm]


smo-041112-1 20 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-281
BPin O
OEt
7a
4.12
4.11
2.45
2.43
2.42
2.41
2.38
2.37
2.35
2.34
1.38
1.37
1.24
1.24
1.01
1.00
2.000
2.083
1.111
15.810
3.088
8
6
4
2
[ppm]


smo-041112-1 21 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-281
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OEt
7a
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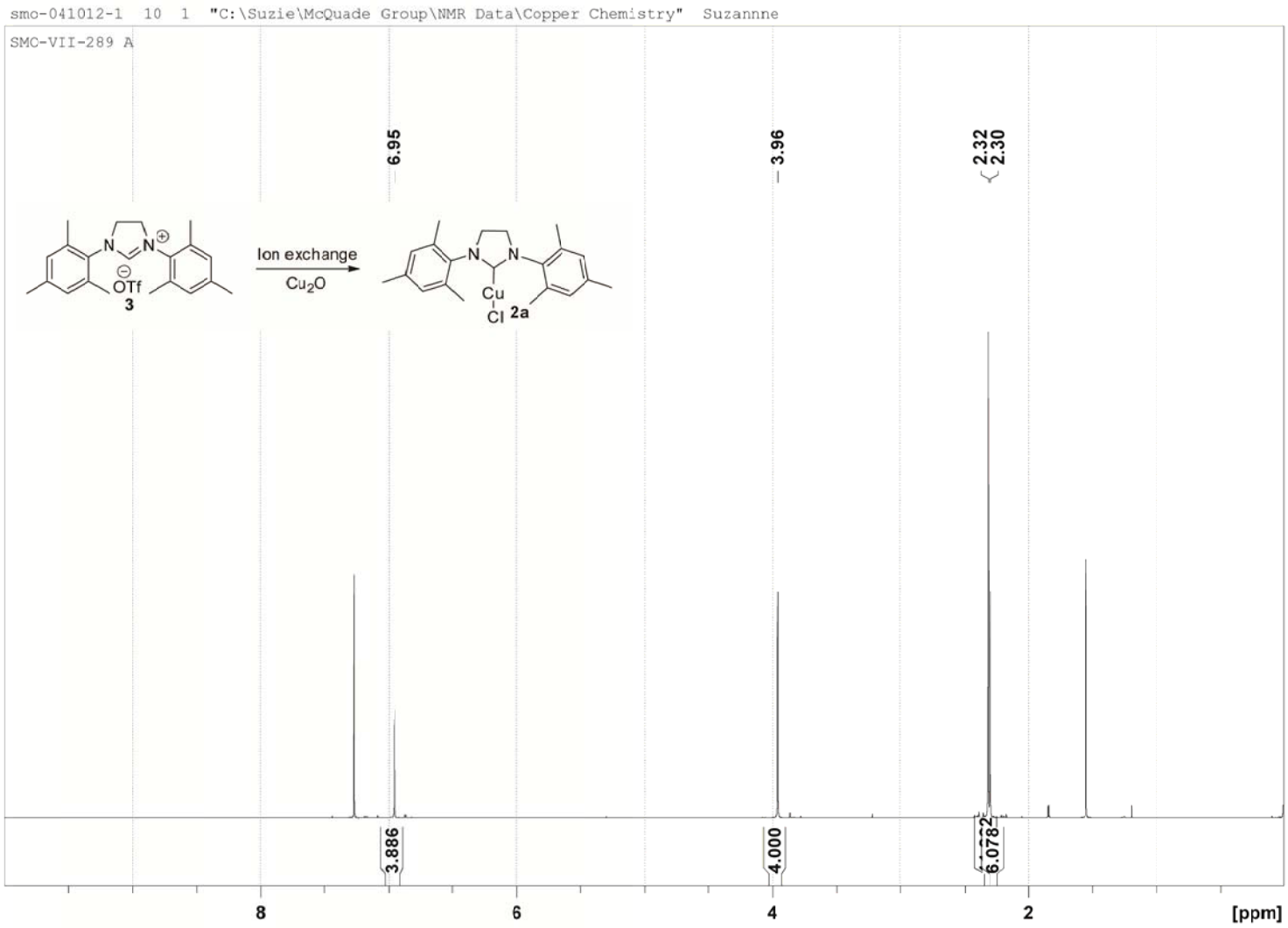
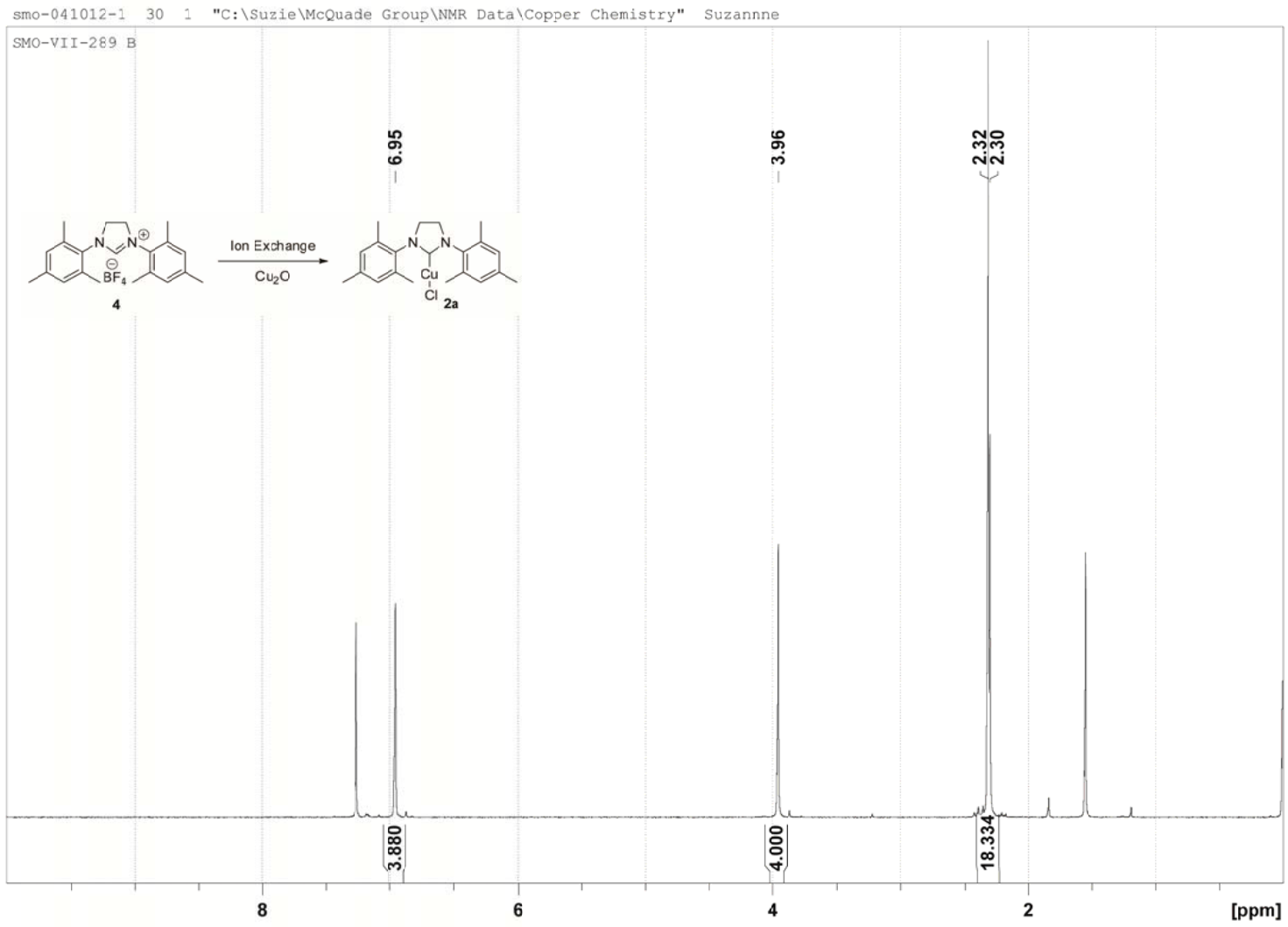
83.13
60.12
37.70
24.72
24.66
15.06
14.30
200
150
100
50
[ppm]


smo-041012-1 10 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMC-VII-289 A
6.95
3.96
2.32
2.30
Ion exchange
Cu2O
OTf
3
Cu
Cl
2a
3.886
4.000
6.0782
8
6
4
2
[ppm]


smo-041012-1 30 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannne
SMO-VII-289 B
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3.96
2.32
2.30
Ion Exchange
Cu2O
BF4
4
Cu
Cl
2a
3.880
4.000
18.334
8
6
4
2
[ppm]